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January 1980 Vol 43 No 1

British Heart Journal

A monthly journal of cardiology
published in association with
the British Cardiac Society

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CUK-H06063-8-P25T24

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ASTM CODEN: BHJUAV 43 (1) 1-124 (1980)

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Case reports are intended to convey only the essential facts of a case, and discussion and bibliography should be kept to a minimum. They should have no more than 3 authors, should not exceed 1500 words, and should contain no more than 2 Figures.

Tables (see also SI units above) must be typed on separate sheets and not in the text. They should be numbered with Arabic numerals and should have a title. Column headings must be clear without lengthy explanatory footnotes.

Illustrations should be identified on the back with Figure number in Arabic numerals and name of author. Legends should be typed on a separate sheet of paper. Figures should be on glossy paper and unmounted unless several are grouped together as in montage. Lettering to be inserted should be indicated lightly in pencil on a transparent overlay. *Diagram, charts,* and *line drawings* should be drawn in indian ink. Only black-and-white *electrocardiograms* make satisfactory blocks, and photographs should be sent rather than original. If several electrocardiograms are grouped in a single Figure, only a few complexes should be shown, and the width should not exceed 5½ inches unless a reduction in scale is feasible. *X-ray pictures* must conform to the standards set out in the Editorial in the Journal, vol. 35, page 1101.

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(2) *Books and other monographs:*
Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology* 1977. Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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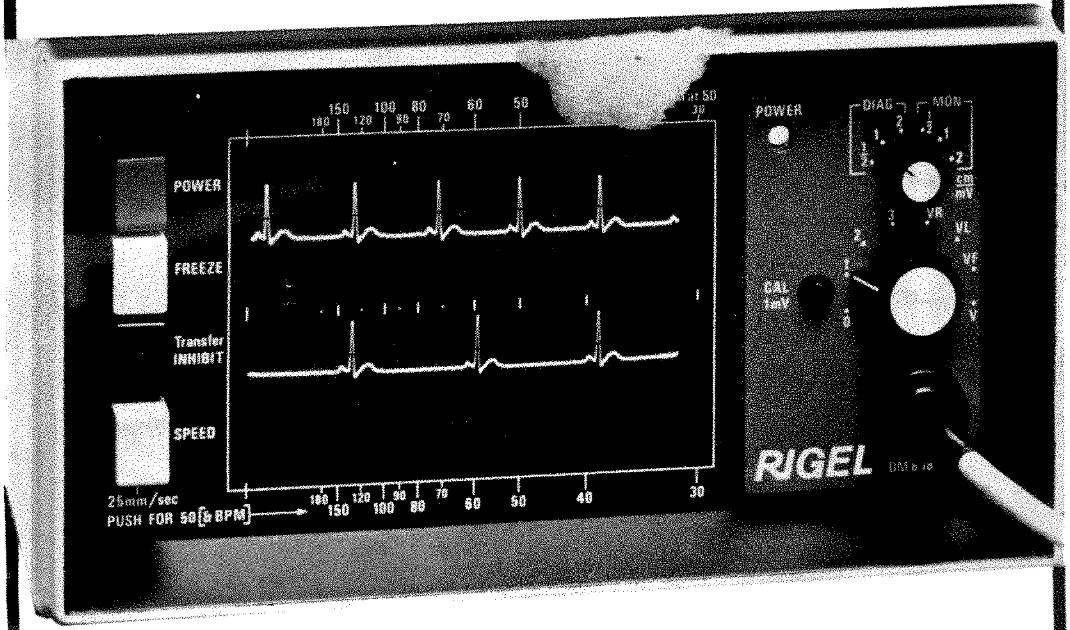

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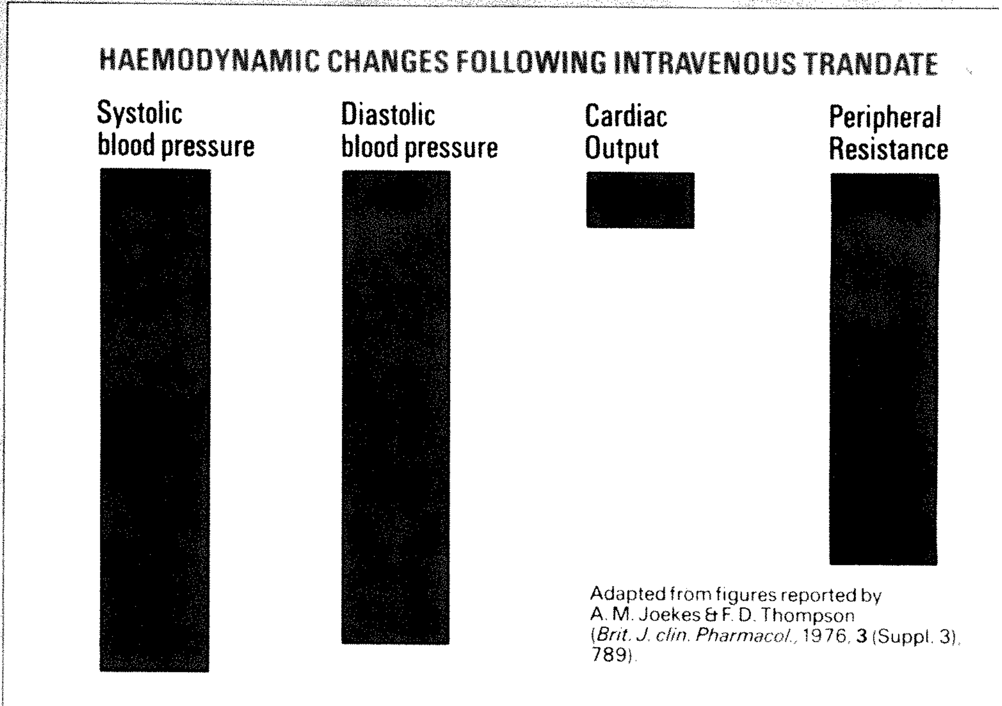

HAEMODYNAMIC CHANGES FOLLOWING INTRAVENOUS TRANDATE

Adapted from figures reported by A. M. Joekes & F. D. Thompson (*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

The above figure shows the mean haemodynamic changes in 14 hypertensive patients given intravenous Trandate 0.5-1.0mg/kg

In essential hypertension the usual haemodynamic changes are increased blood pressure and peripheral resistance while cardiac output remains normal.

The authors of the above trial reported:
"Although there are striking changes in the blood pressure, this can be largely attributed to a fall in peripheral resistance with little change in pulse rate, stroke volume or cardiac output."

INTRAVENOUS TRANDATE
reduces blood pressure and peripheral resistance
without significantly affecting cardiac output

come down fast...

INJECTION

Trandate Injection provides rapidly effective control of hypertensive emergencies

AS A BOLUS INJECTION...

"Labetalol given intravenously is highly effective for the acute reduction of blood pressure. In this series no serious side effects were encountered and the drug seems particularly suitable for use in hypertensive emergencies." (Rosei, E. A. et al, *Clin. Sci. mol. Med.*, 1976, **51**, 497s)

OR AS A CONTINUOUS INFUSION...

"Labetalol, given slowly by graded intravenous infusion, with continuous monitoring of arterial pressure, is our current treatment of choice in hypertensive emergencies." (Brown, J. J. et al, *Lancet*, 1977, **i**, 1147)

Subsequent treatment can be continued with the same drug given orally

"A practical advantage associated with labetalol is that oral treatment can be instituted immediately after using the intravenous form." (Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

"There are many advantages to using a compound that can be given intravenously to control blood pressure in patients with small vessel disease or impaired renal function, which is then available for long-term oral therapy." (Joekes, A. M. & Thompson, F. D., *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789–793)

Trandate Tablets provide effective therapy in all grades of hypertension – including the difficult cases

"In this study (oral) labetalol reduced the blood pressure significantly in a group of patients with severe, drug-resistant hypertension." (Morgan, T. et al, *Med. J. Australia*, 1978, **i**, 393)

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PRODUCT INFORMATION

PRESENTATION

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Trandate Tablets are indicated for the oral treatment of all grades of hypertension, mild, moderate and severe. Trandate Injection is indicated when rapid control of blood pressure is essential.

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Trandate Tablets:

Adults: The initial dosage should not usually exceed 100mg 3 times daily. Adjustment of dosage should be gradual. Most cases are controlled with 600mg per day or less, but severe cases may require up to 2,400mg daily. Administration should be after a main meal.

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Adults: When rapid reduction of blood pressure is essential a dose of 50mg of Trandate should be given by intravenous injection over at least one minute. This may be repeated, if necessary, at 5-minute intervals but the total daily dose should not exceed 200mg. Alternatively it may be given by intravenous infusion. For this 2 ampoules of Trandate Injection are diluted to 200ml with sodium chloride and dextrose injection BP. This is infused at a rate of 2ml/minute until a satisfactory response is obtained when the infusion should be stopped. For most patients the effective dose is from 50 to 200mg but in phaeochromocytoma up to 300mg may be necessary.

Patients should be in the supine position when Trandate Injection is given and they should not stand or sit up within 3 hours of starting the administration. Once controlled, blood pressure reduction can be maintained with Trandate Tablets at a starting dose of 200mg 3 times daily.

Children: Not applicable.

For information on the use of Trandate with other drugs or for transfer to Trandate from other antihypertensive agents, see respective Data Sheets.

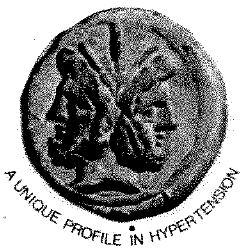
CONTRA-INDICATIONS, WARNINGS, ETC.

Trandate should not be given to patients with uncontrolled or digitalis-resistant heart failure, or with atrioventricular block. Caution is necessary in asthmatic patients or others prone to bronchospasm. Patients with severe liver damage will probably require lower doses of Trandate than usual. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.

Trandate Injection may cause excessive postural hypotension if patients are allowed to assume the upright position within 3 hours of administration.

Trandate Tablets may cause symptoms of postural hypotension if initial dosage is too high or increased too rapidly, but they are uncommon, except at very high doses, if used as recommended. Mild and usually transient side effects include: headache, tiredness, dizziness, depressed mood, lethargy, difficulty in micturition, epigastric pain and nausea and vomiting. Tingling in the scalp has occasionally occurred but is usually transient. Rarely, a lichenoid rash has been reported which disappears on drug withdrawal. Other skin rashes, blurring of vision, eye irritation and cramps have been reported but have been difficult to relate directly to Trandate treatment.

Warning: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the drug was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.



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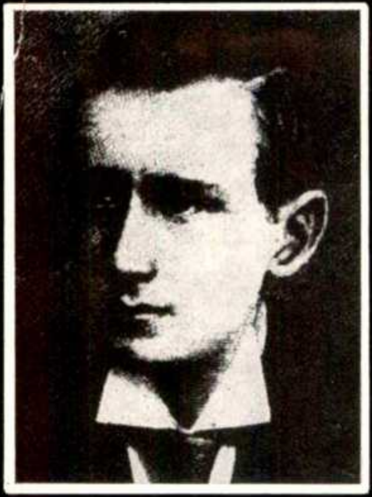

Guglielmo Marconi
(Bologna 1874-Roma 1937)

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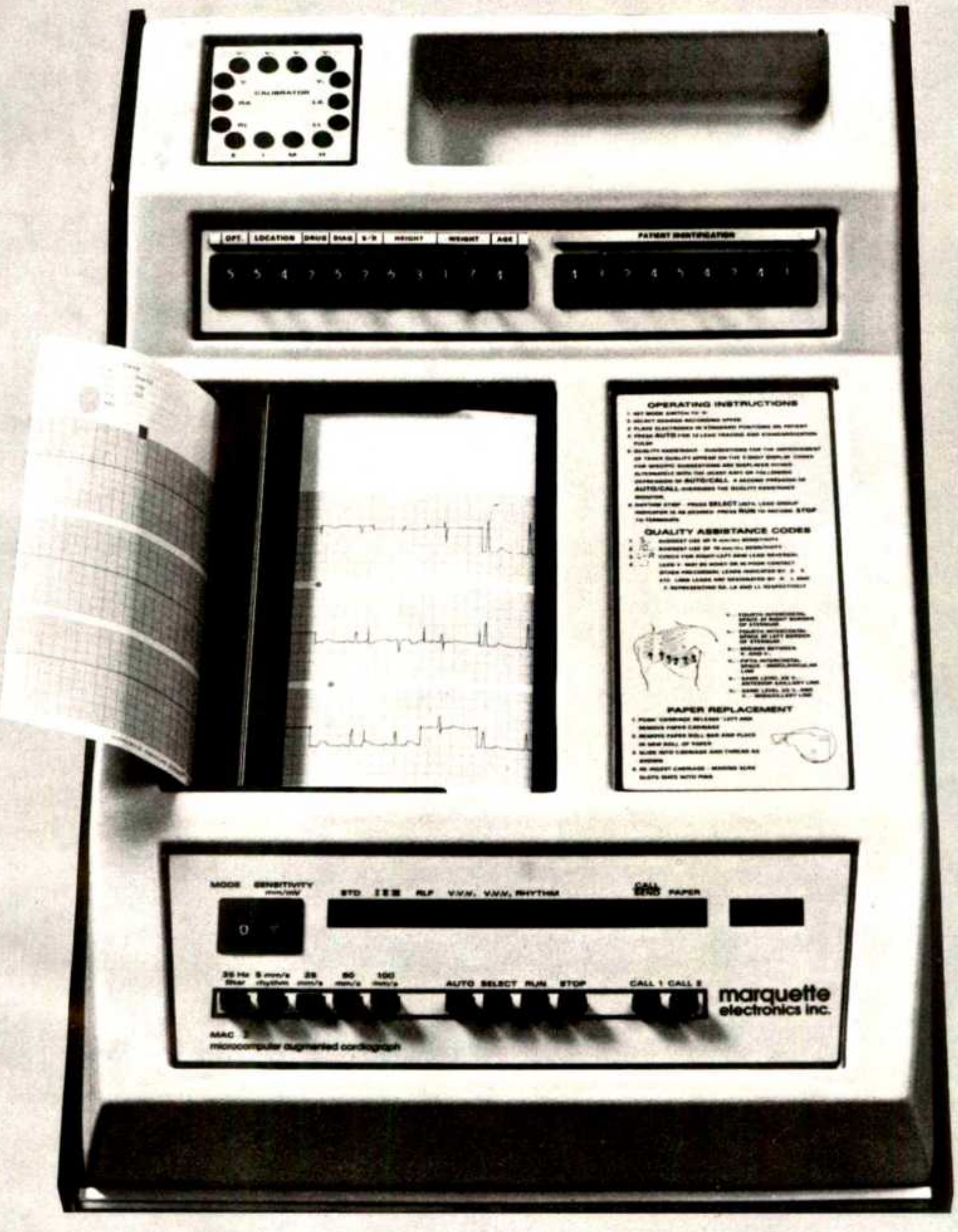

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Corgard prescribing information

PRESENTATION

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Indications

For the long-term management of essential hypertension, either alone or in combination with other anti-hypertensive agents.

DOSAGE AND ADMINISTRATION

Initially 80 mg once daily. This dose may be increased by 80 mg increments at weekly intervals until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have occasionally been used. In some patients it may be necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agents in conjunction with nadolol in order to achieve satisfactory response. Dosage should be individually titrated.

Nadolol may be given in a once daily dosage without regard to meals.

Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent.

Contra-indications

Like other drugs in this class, nadolol is contra-indicated in bronchial asthma; allergic rhinitis during the pollen season; sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure; during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors.

Warnings

Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency.

The normal precautions associated with the use of beta-adrenergic blockers should be followed.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenergic blocker should be gradual.

Nadolol should be used with caution in patients with impaired renal or hepatic function.

The safety of nadolol in pregnancy has not yet been established, and it should only be given to nursing mothers if deemed essential.

Side-effects

These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. They include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insufficiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically.

LEGAL CATEGORY

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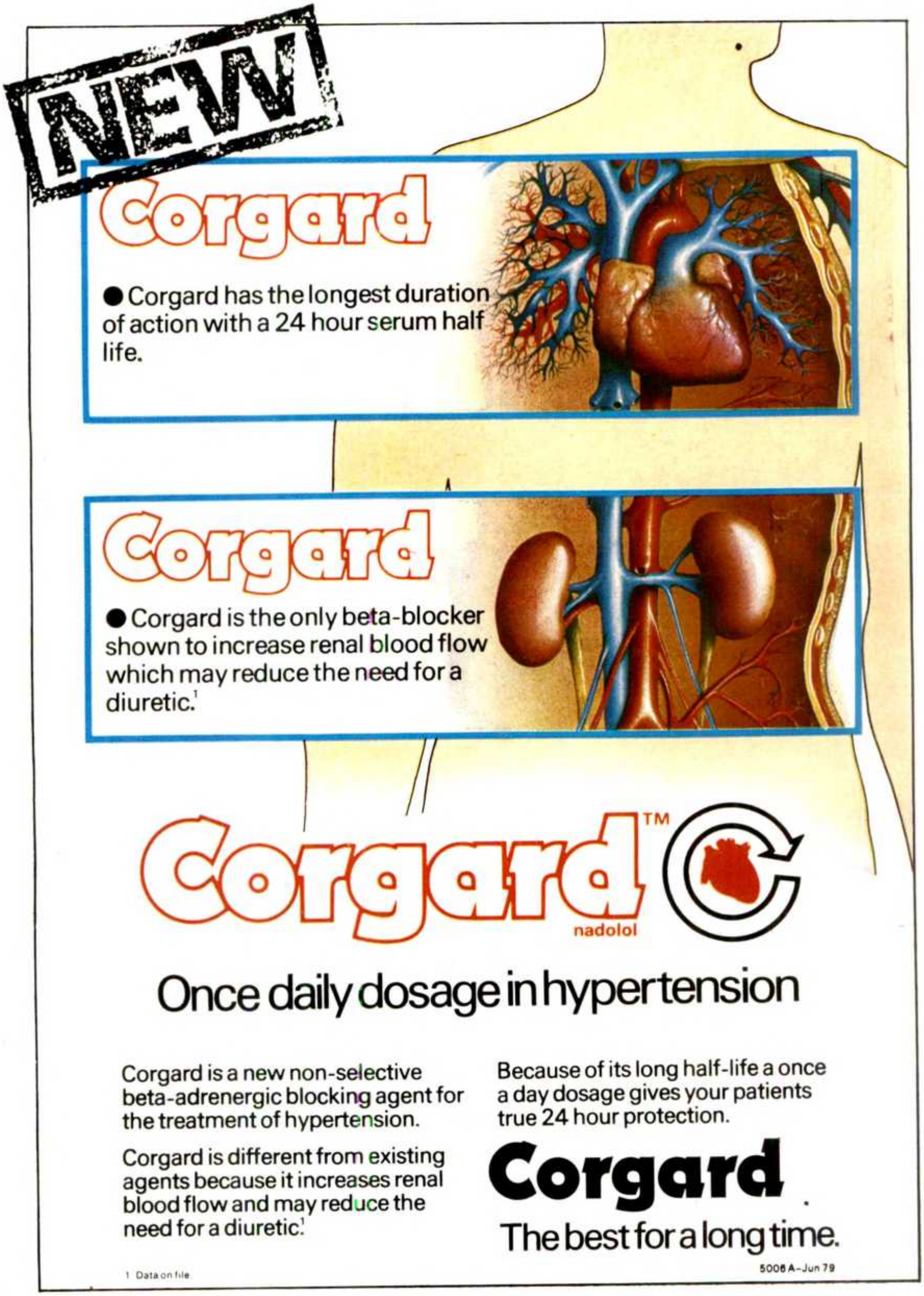

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[1] Data on file

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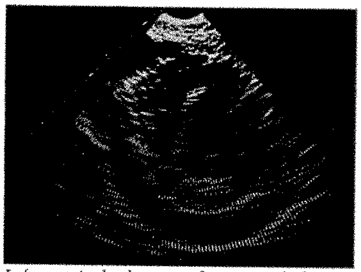
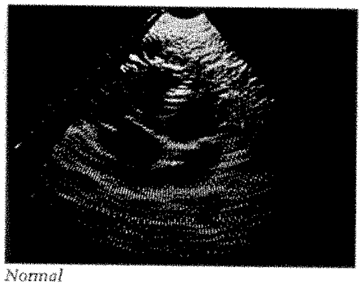
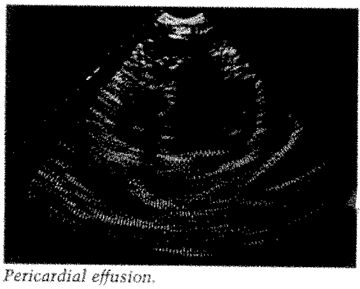


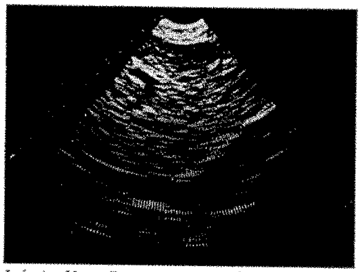
Left ventricular hypertrophy, pericardial effusion.



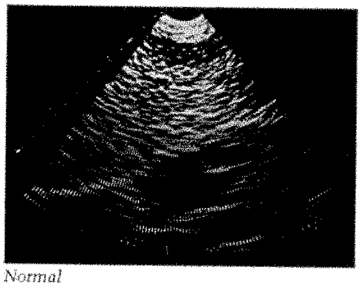
Normal



Pericardial effusion.



Inferior Vena Cava entering right atrium.



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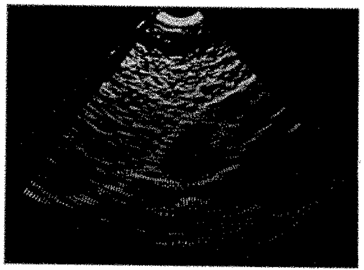
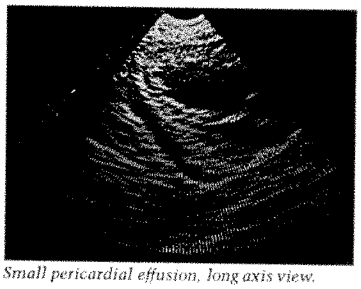
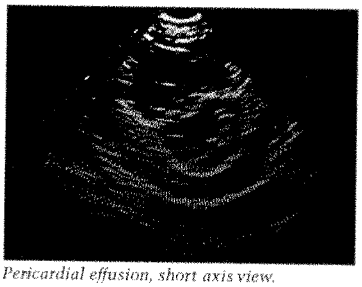


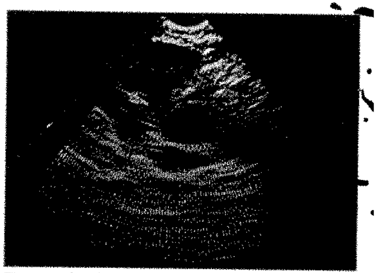
Tricuspid valve vegetation.



Small pericardial effusion, long axis view.



Pericardial effusion, short axis view.



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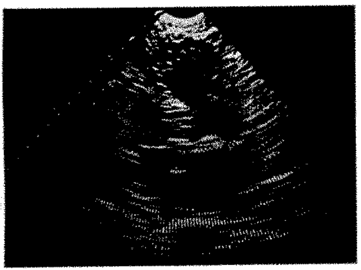
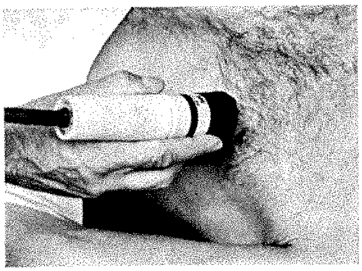
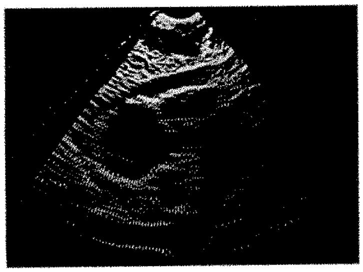
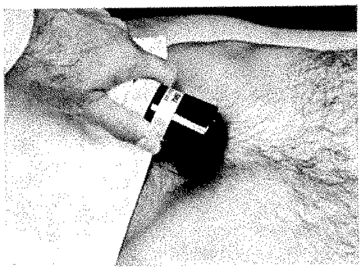
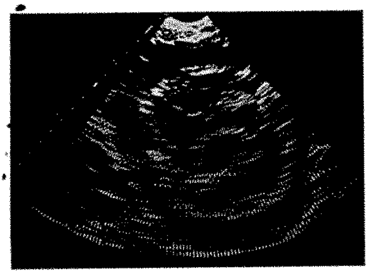

Mitral valve prolapse.


Apex Four Chamber Views


Pericardial effusion.


Subxyphoid Views


Left ventricular hypertrophy pericardial effusion, short axis.

Parasternal Views

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BRITISH HEART JOURNAL

Volume 43

1980

BRITISH MEDICAL ASSOCIATION, TAVISTOCK SQUARE, LONDON·WC1H 9JR

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Effect of intravenous propranolol on QT interval
A new method of assessment

J R MILNE, A J CAMM, D E WARD, R A J SPURRELL

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SUMMARY Changes in the QT and QTc intervals were studied in 16 patients by atrial pacing at rates of 100, 130, and 150 beats/minute. In all patients the measured QT shortened when the atrial paced rate was increased, but when corrected for heart rate the QTc lengthened. Intravenously administered propranolol produced a bradycardia and a lengthening of the QT interval in 15 of the 16 patients studied. When the QT interval was corrected for heart rate using Bazett's formula the QTc was shortened in 13 patients, unchanged in one, and lengthened in two. However, when the QT interval was measured at identical atrial paced rates the QT of the 15 patients studied was lengthened in 10 and unchanged in five. In none was the QT interval shortened. These results show firstly that Bazett's formula is unsuitable for correction of QT interval changes induced by atrial pacing, and secondly that, though intravenously administered propranolol usually produces a shortening of the QTc, when its effect is assessed directly by using an identical atrial paced rate the QT interval usually lengthens, or may remain unchanged, but never shortens. It is suggested that the formal assessment of drug induced QT interval changes should be made at identical atrial paced rates.

Prolongation of the QT interval may occur after the administration of drugs such as quinidine,[1] amiodarone,[2] disopyramide,[3] the tricyclics,[4] and the phenothiazines.[5] The effect of propranolol on the QT interval remains controversial. Previous studies suggest that though it lengthens the measured QT, correction for heart rate by Bazett's hyperbolic correction factor[6] shows that the QTc is usually shortened.[7 8]

As such drugs may also cause changes in the heart rate, when assessing their effect on the QT interval the use of a correction factor for heart rate becomes necessary. Of the many formulae available Bazett's hyperbolic correction factor which corrects to a rate of 60 beats/min has been most readily accepted for use because it is simple to apply. In order to overcome the necessity for rate correction a new method has been devised for the assessment of drug induced QT changes using atrial pacing at identical rates before and after the administration of propranolol. This allows a direct comparison of these changes to be made and precludes the need for a correction factor. The purpose of this study was twofold. Firstly, to test the validity of Bazett's hyperbolic correction factor for QT changes induced by atrial pacing, and, secondly, to assess the effect of intravenously administered propranolol on the QT interval both during sinus rhythm and at identical atrial paced rates.

Received for publication 6 March 1979

Patients and methods

Sixteen patients were studied, all of whom were undergoing routine catheterisation. The age, sex, diagnosis, electrocardiogram, and chest *x*-ray findings are recorded in Table 1. They were volunteers who had been informed that this study was not a necessary part of their investigations. All the patients had a normal QT interval, were in sinus rhythm at the time of the study, and had been so for at least 24 hours before the study was undertaken. Each was capable of 1:1 atrioventricular conduction at a rate of 150 beats/min. The QRS complexes were normal and in no instance was there evidence of either a partial or complete bundle-branch block pattern. Patients with prominent U waves were excluded.

The patients had undergone cardiac catheterisation at least 24 hours before this investigation and at the time of catheterisation a bipolar pacing electrode was left high in the right atrium. All cardioactive drugs were stopped at least 24 hours before the study was performed. The investigation was

Table 1 *Clinical data*

Case no.	*Age (y)*	*Sex*	*Diagnosis*	*Electrocardiogram*	*Chest x-ray*
1	37	M	Coronary artery disease	Non-specific T wave changes	Normal
2	39	M	Angina, normal coronary arteries	Non-specific T wave changes	Normal
1	37	M	Coronary artery disease	Non-specific T wave changes	Normal
3	57	M	Coronary artery disease	Normal	Normal
4	58	M	Coronary artery disease	Normal	Normal
5	45	M	Coronary artery disease	Old inferior infarct	Normal
6	15	F	Re-entry nodal tachycardia	Normal	Normal
7	39	M	Re-entry nodal tachycardia	Normal	Normal
8	39	M	Lown-Ganong-Levine syndrome	Short PR interval	Normal
9	47	M	Lown-Ganong-Levine syndrome	Short PR interval	Normal
10	50	M	Asystolic episodes, uncertain aetiology	Normal	Normal
11	65	M	Mitral regurgitation, coronary artery disease	Normal	Cardiomegaly
12	41	M	Concealed VA tract, ventricular tachyarrhythmias	Short PR interval	Normal
13	31	M	Spontaneous ventricular fibrillation	Normal	Normal
14	44	M	Sinuatrial disease	Normal	Normal
15	17	M	Hyperkinetic heart syndrome	Normal	Normal
16	31	F	Hyperadrenergic syndrome	Sinus tachycardia	Normal

undertaken on the open ward, with the patient in a semi-recumbent position lying at approximately 30° to the horizontal. A butterfly needle was inserted into an arm vein several minutes before the recordings were made. The electrocardiographic recordings were taken on a four-channel Elema mingograf with time markings at one second intervals, at a paper speed of 100 mm/s. As changes in the T wave vector may masquerade as changes in the QT interval three more-or-less orthogonal leads were recorded, as suggested by Pipberger and Tanenbaum.[9] The QT interval was measured from the earliest QRS deflection to the terminal T wave deflection on any lead, and the cycle length was taken as the interval between the peaks of the two preceding R waves. When the end of the T wave was indistinct either because of a poor baseline, or other artefact, the trace was discarded. At high atrial paced rates the pacing stimulus artefact or the P wave fused with the preceding T wave rendering the measurement of the QT interval impossible. This was overcome by switching off the pacemaker and measuring the QT interval of the last of a sequence of atrial paced beats. Atrial pacing was undertaken for approximately 20 seconds before the pacemaker was switched off. The QT interval was measured during sinus rhythm and, when possible, at atrial paced rates of 100, 130, and 150 beats/min. An intravenous injection of propranolol 0·1 mg/kg body weight was given over three minutes and the QT interval was again measured during sinus rhythm and at the same atrial paced rates between five and 10 minutes later. The measured QT interval was then corrected to a heart rate of 60 beats/min using Bazett's formula, with which the corrected QTc is derived by dividing the measured QT by the square root of the RR interval in seconds, that is

$$\text{QTc} = \frac{\text{measured QT}}{\sqrt{\text{RR interval (s)}}}$$

Results

Atrial pacing at higher rates shortened the measured QT and lengthened the rate corrected QT. The results are displayed graphically in Fig. 1. Five of the 16 patients studied were not included as two

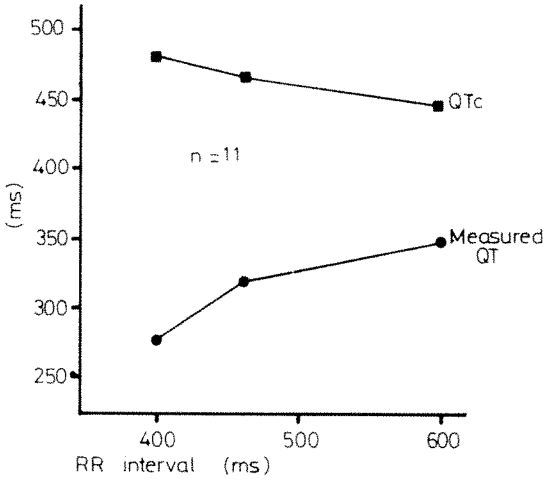

Fig. 1 *Mean measured QT and rate corrected QT intervals for atrial paced rates of 100, 130, and 150 beats/minute.*

had a sinus rate of greater than 100 beats/min, and in three the end of the T wave was not clearly delineated. Intravenous propranolol produced a relative bradycardia and a lengthening of the measured QT in 15 patients. One patient had a relative tachycardia and a shortening of the measured QT (Fig. 2). When the measured QT was corrected for heart rate intravenous propranolol produced a shortening of the QTc in 13 patients, no change in one, and a slight lengthening in two. Fig. 3 shows the effect of intravenous propranolol on the sinus rate and measured QT of an individual patient. The sinus cycle length increased from 545 to 645 ms, and the measured QT from 320 to 345 ms. However, the QTc using Bazett's formula shortened from 433 to 429 ms. When fixed atrial pacing with a cycle length of 375 ms was used (Fig. 4) intravenous propranolol lengthened the measured QT from 300 to 325 ms. The effect of intravenous propranolol on the measured QT and rate corrected QT during sinus rhythm and at various atrial paced rates for the same patient are shown in Fig. 5.

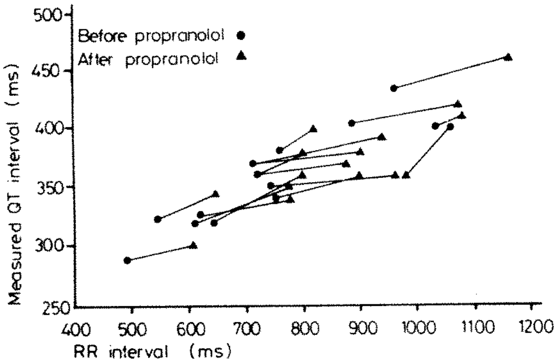

Fig. 2 *Effect of intravenous propranolol on sinus cycle length and measured QT interval.*

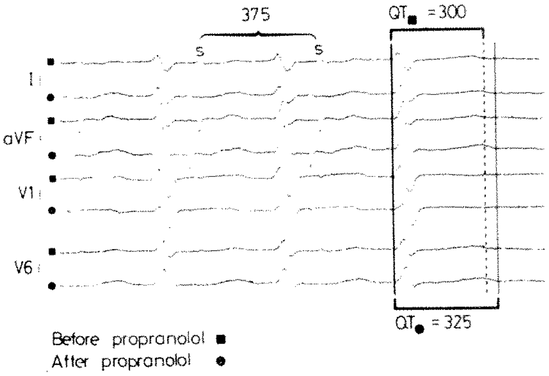

Fig. 4 *Format of this illustration is similar to Fig. 3. However, atrial pacing with a cycle length of 375 ms has been employed. Propranolol has increased the QT interval from 300 to 325 ms.*

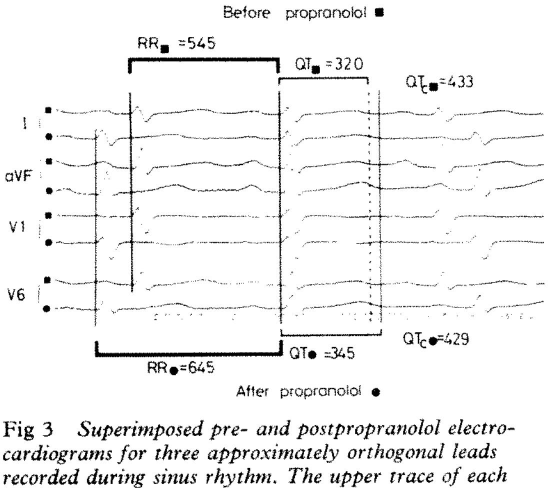

Fig 3 *Superimposed pre- and postpropranolol electrocardiograms for three approximately orthogonal leads recorded during sinus rhythm. The upper trace of each pair was recorded before propranolol and the lower after. The tracings are aligned at the onset of second QRS deflection. The end of the T waves in the control state and postpropranolol state are represented by the vertical interrupted line and the thin vertical continuous line, respectively. Propranolol has produced a relative bradycardia and increased the measured QT, though the QTc is shortened.*

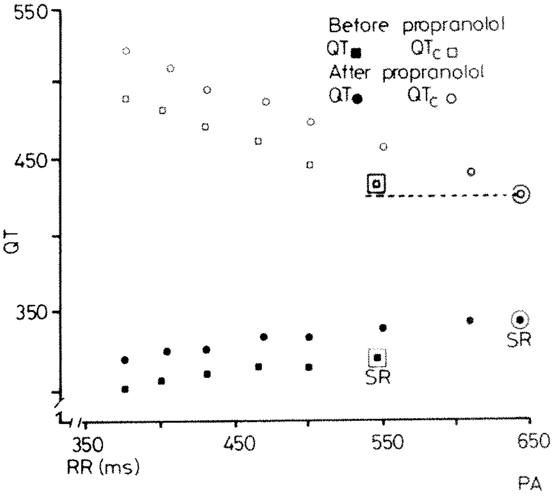

Fig. 5 *Measured QT and QTc of an individual patient are shown against the cycle length both during sinus rhythm and at atrially paced rates before and after the administration of propranolol. During sinus rhythm and at each atrially paced rate the QT interval has been lengthened by intravenous propranolol.*

With atrial pacing the measured QT shortened linearly as the rate increased but when corrected for rate the QT lengthened both before and after the administration of propranolol. However, at each identical atrial paced rate both the measured QT and rate corrected QT were similarly lengthened by the administration of propranolol.

At identical atrial paced rates 10 patients showed a prolongation of the QT and five showed no change after the administration of propranolol. In no instance was the QT shortened by propranolol (Fig. 6). These results include 13 patients who were paced at 100 beats/minute, and one each at 120 and 130 beats/minute because their resting sinus rates were greater than 100 beats/minute. The results discussed above are set out in Table 2.

Discussion

The QT interval of the standard electrocardiogram is a clinical measurement of ventricular depolarisation and repolarisation. As the acute administration of intravenous propranolol has no effect on the QRS complex width,[8] any change of this variable reflects a change in the duration of ventricular repolarisation. Many conditions in which a long QT interval occur are associated with syncope and sudden death.[10-12] Lengthening of the QT interval may increase the vulnerable period of the ventricular myocardium, during which ventricular arrhythmias may be precipitated by a ventricular premature beat.[13 14] Therefore, drugs which shorten the QT interval may, theoretically, have therapeutic advantages in these conditions. Propranolol is one such drug which shortens the QTc though this effect is variable. Stern and Eisenberg[7] found that though the measured QT increased in 11 patients, decreased

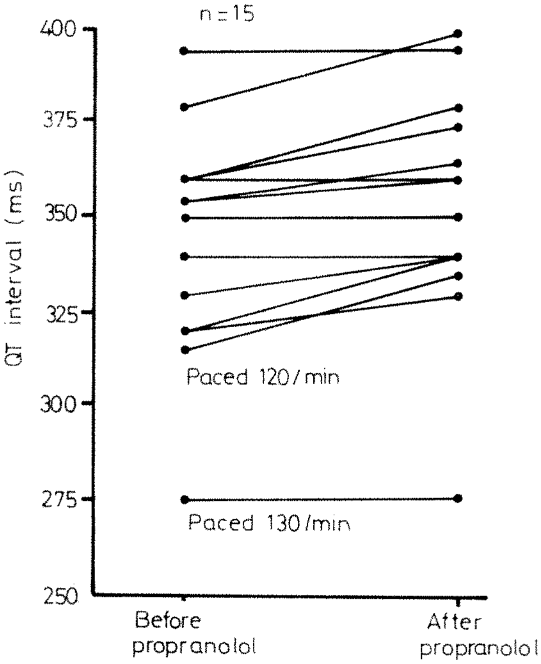

Fig. 6 *Effect of intravenous propranolol on the measured QT at identical paced rates. Thirteen patients were paced at 100 beats/minute and one each at 120 and 130 beats/minute as their sinus rates were greater than 100 beats/minute.*

Table 2 *Cycle length, measured QT, QTc in sinus rhythm, and atrially paced QT before and after propranolol*

Case no.	*Cycle length (ms)*		*Measured QT*		*QTc (sinus rhythm)*		*Atrially paced QT*	
	Before	*After*	*Before*	*After*	*Before*	*After*	*Before*	*After*
1	490	605	275	300	393	385	275 paced at 130/min	275
2	1060	980	400	360	388	364	340	340
3	720	880	360	370	424	405	350	350
4	710	900	370	380	439	400	360	375
5	750	900	340	360	393	379	330	340
6	545	645	320	345	433	429	315 paced at 120/min	335
7	965	1170	435	460	443	434	395	395
8	740	960	350	360	407	367	330	340
9	710	940	370	390	421	402	355	360
10	1030	1080	400	410	396	392	380	400
11	760	820	380	400	436	442	360	380
12	720	800	360	380	425	425	360	360
13	640	800	320	360	400	403	320	340
14	620	775	325	340	413	386	320	330
15	610	775	320	350	410	398	Unable to measure	
16	885	1075	405	420	430	405	355	365

in four, and did not change in six after acutely administered propranolol, when corrected for rate the QT shortened in 20 and was unchanged in one. Seides *et al.*[8] found that the QTc shortened in nine of 16 patients and was unchanged in seven. In this study the QTc was similarly shortened in 13 of 16 patients. In the light of the effect on the QTc interval propranolol has been recommended as treatment for the long QT syndrome, with some success,[15–17] but its efficacy is by no means universal.[18]

Though it is important to assess accurately the effect of drugs on the QT interval, all previous comparisons have been made by applying a rate correction factor.

Many correction factors have been suggested.[6 19–23] Of these Bazett's formula[6] has been most widely used. In Bazett's formula the relation of the measured QT to cycle length is curvilinear rather than linear and though this is marginally less accurate for resting physiological heart rates it is more accurate at higher heart rates where a curvilinear relation applies.[23] Thus, Bazett's formula may appear to be relevant to our study where high rates of atrial pacing have been used. But our results show that at atrial paced rates Bazett's hyperbolic correction factor overcorrects for QT changes resulting in a spuriously long rate corrected QT interval. In defence of Bazett's formula, his conclusions were drawn from data taken from patients studied under physiological conditions at rest and after exercise unlike our patients who were atrially paced, which may not reflect the same haemodynamic and physiological state. It has been shown for instance that during exercise and the infusion of intravenous isoprenaline the PR interval shortens as the heart rate increases[24–26] whereas when the heart rate is artificially increased by atrial pacing the PR interval lengthens.[27] It is possible that atrial pacing may have a similar unphysiological effect on the QT interval and that Bazett's formula, though applicable to physiological changes in heart rate, is unsuitable for correcting the measured QT for changes in heart rate induced by atrial pacing.

This study was designed to circumvent the use of a correction factor by directly comparing the measured QT before and after the administration of propranolol at identical atrial paced rates. The change in the measured QT interval induced by atrial pacing is not necessarily equivalent to the change seen after spontaneous or drug-induced rate changes. After the administration of a drug which produces sinus bradycardia it is necessary to overpace the atria by a proportionately greater increment in order to achieve the same paced rate for comparison. This may itself introduce artefactual error which cannot be avoided by this new method.

Our results show that when propranolol produced a bradycardia the measured QT interval lengthened. One patient had a relative tachycardia after intravenous propranolol. Reflex sympathetic activity has been described after acutely administered beta-adrenergic blocking drugs and exercise,[28] and it is possible that this was the overriding effect in this patient. In the 15 patients who had bradycardia, though the QTc tended to shorten, the QT interval measured at identical atrial paced rates usually lengthened or remained unchanged but in no instance was it shortened. When comparing drug induced changes on cardiac conduction intervals it has become customary to make comparison between measurements made at identical paced rates in order to exclude changes resulting from alterations in heart rate after drug administration. This principle has been applied in this study to QT changes and has produced results consistent with those reported by Raine[29] on the QT changes secondary to long-term beta-blockade with propranolol. Comparable results have also been found by Bertil Olsson (1978, personal communication) using similar methods and acutely administered metoprolol.

These results suggest that it may not be the effect of propranolol on the QT interval, which it usually prolongs, that makes this drug a useful therapeutic agent in the long QT syndromes: direct anti-sympathetic activity, and its ability to increase the threshold for ventricular fibrillation,[30] may be more important. Using our technique, the effect of intravenously administered propranolol on the QT interval, in patients with the long QT syndrome, is not yet known; findings under such circumstances may be different from those in our study.

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Br Heart J 1980; **43**: 7–13

'Dual atrioventricular nodal pathways' in patients with Wolff-Parkinson-White syndrome*

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SUMMARY 'Dual atrioventricular nodal pathways' were found in five patients who also had the Wolff-Parkinson-White syndrome. All five patients had a re-entrant tachycardia that used the atrioventricular node for conduction in the anterograde direction and an accessory atrioventricular pathway for conduction in the retrograde direction. One of the patients also had a re-entrant tachycardia that originated within the atrium or the atrioventricular node. Dual atrioventricular nodal pathways were identified in three of the five patients during their first electrophysiological study because the effective refractory period of the accessory atrioventricular pathway in the anterograde direction was longer than the effective refractory period of the *fast* atrioventricular nodal pathway. In the other two patients the dual atrioventricular nodal pathways were found only after operative division of an accessory atrioventricular pathway.

Re-entrant tachycardia that uses an accessory pathway may be cured by operative division of the accessory pathway. Tachycardia resulting from re-entry within the atrioventricular node cannot be cured by an operation unless the normal conduction system is divided and a permanent pacemaker implanted. These five patients indicate the importance of determining the aetiology of tachycardia by studying the tachycardia itself and not only the type of atrioventricular conduction present.

Tachycardia that begins and ends suddenly, and during which the QRS morphology on the electrocardiogram is normal is commonly called paroxysmal supraventricular tachycardia.[1-3] In patients with the Wolff-Parkinson-White syndrome, paroxysmal supraventricular tachycardia is a re-entrant arrhythmia which uses the atrioventricular node for conduction in the anterograde direction and an accessory pathway for conduction in the retrograde direction.[4-6] Paroxysmal supraventricular tachycardia may also be the result of re-entry within the atrioventricular node.[7-9] In this latter case dual atrioventricular nodal pathways are usually shown by testing with the extrastimulus technique in the atrium. In this report we describe five patients with the Wolff-Parkinson-White syndrome who also had dual atrioventricular nodal pathways. This study shows the importance of basing criteria for diagnosing tachycardias on the behaviour of the tachycardia rather than on the type of atrioventricular conduction that is present.

Patients and methods

The patients were among those referred to the Duke University Medical Center for treatment of Wolff-Parkinson-White syndrome and paroxysmal arrhythmias between July 1974 and March 1978. All five patients had a delta wave on the QRS complex of electrocardiograms recorded during sinus rhythm. All five patients also had spontaneous occurrence of a regular tachycardia during which the QRS complex on the electrocardiogram was normal. Patients were identified by reviewing pre-admission records and results of electrophysiological studies performed while they were in hospital. When available, electrophysiological studies performed after surgical correction of ventricular pre-excitation were also reviewed. Illustrations from records of cases 4 and 5 have been previously published.[5 10]

All patients gave informed consent before investigation. Complete medical history, physical examina-

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* Supported in part by grants from the General Clinical Research Centers Branch, Division of Health Resources, and from the National Institutes of Health, Bethesda, Maryland. This work was done during the tenure of Dr Benditt as a Fellow of the Medical Research Council of Canada. Dr Pritchett is the recipient of a NHLBI Young Investigator Research Award. This work was done during Dr Gallagher's tenure as an established investigator of the American Heart Association.

Received for publication 13th September 1979

tion, chest *x*-ray films, and electrocardiograms were obtained on admission. Antiarrhythmic treatment was discontinued at least 48 hours before study.

Laboratory techniques used in these studies have been reported previously.[5 11 12] Electrode catheters were positioned to record simultaneously from the right atrium, coronary sinus, bundle of His, and right ventricle. Heparin (100 units/kg) was given intravenously after catheters were positioned. Atrioventricular conduction in the anterograde and retrograde directions was studied with fixed-rate pacing and the extrastimulus technique. When using the extrastimulus technique, every eighth driven stimulus was followed by a premature stimulus at progressively shorter coupling intervals until the refractory period of the chamber was reached. Re-entrant tachycardias which occurred spontaneously during study or which were induced by programmed stimulation were studied with endocardial mapping and programmed premature beats. Endocardial mapping was performed by recording from the right atrium and atrial septum with a specially constructed bipolar electrode catheter[13] and by recording from the left atrium with a quadripolar catheter in the coronary sinus. Endocardial mapping was used to locate the site of earliest atrial activation during re-entrant tachycardia. Premature ventricular stimuli were coupled to every eighth beat of the tachycardia by programmed stimulation and induced throughout the cardiac cycle.[14] These premature stimuli were used to show atrial pre-excitation (early retrograde atrial activation).

Standard surface electrocardiogram leads and intracardiac electrograms were recorded on magnetic tape at 3¾ in/s and written on paper at 200 or 250 mm/s by a Siemens Mingograf ink-jet recorder. Refractory periods were measured with an interactive computer programme.[15] Using this programme independent observers have made measurements that were reproducible within 2 ms.

Definitions

S_1, A_1, H_1, and V_1 respectively refer to the stimulus, atrial electrogram, His bundle electrogram, and ventricular electrogram of the basic drive complex. A_2, H_2, and V_2 refer to the atrial electrogram, His bundle electrogram, and ventricular electrogram caused by the extrastimulus S_2. A_{E1} and H_{E1} refer to the atrial electrogram of the first atrial echo beat and the His bundle electrogram that it initiates. All echoes specifically referred to in *this* paper were initiated by conduction in the retrograde direction over an accessory atrioventricular pathway.

Accessory atrioventricular pathway: An accessory atrioventricular muscle bundle.[16]

Re-entrant tachycardia which used the atrioventricular node for conduction in the antegrade direction and an accessory atrioventricular pathway for conduction in the retrograde direction. A tachycardia which satisfied at least one of the following criteria:

(1) The direction of atrial activation (determined using the technique of endocardial mapping) was retrograde and eccentric,[13] that is atrial activation appeared not to begin at the atrioventricular node.

(2) Bundle-branch block in the ventricle with the accessory atrioventricular pathway lengthened the ventriculoatrial conduction time by 25 ms or more.[17]

(3) Premature ventricular beats pre-excited the atrium during tachycardia at a time when the His bundle was refractory[14] and the sequence of atrial activation of the pre-excited P wave was identical to the sequence recorded during tachycardia.

Dual atrioventricular nodal pathways: A type of atrioventricular nodal function characterised by a discontinuous curve of H_1–H_2 intervals generated by the extrastimulus coupling intervals (A_1–A_2).[18] This definition is based on the characteristics of atrioventricular nodal refractoriness, which is indirect evidence. No anatomical evidence of distinct, specialised conduction pathways has been reported.

Published definitions have been used to define the effective and functional refractory periods of the accessory atrioventricular pathway[19], the atrium,[20] the fast atrioventricular nodal pathway[18], and the slow atrioventricular nodal pathway.[18]

Results

All five patients had a re-entrant tachycardia that used the atrioventricular node for conduction in the anterograde direction and an accessory atrioventricular pathway for conduction in the retrograde direction. In cases 1 and 2 (Table) continuous block of conduction in the anterograde direction over the accessory pathway was present with the pacing cycle length used to measure refractory periods. All basic driven and premature complexes at all coupling intervals were conducted with normal QRS appearances. In case 1 tachycardia was initiated by premature atrial stimuli that were conducted over either the fast or slow atrioventricular nodal pathway (Fig. 1). In case 2 tachycardia was initiated only by premature impulses that were conducted over the slow atrioventricular nodal pathway (Fig. 2). For example, premature stimuli with a coupling interval of 320 ms were repeated four times, and H_1–H_2 intervals of 409, 352, 343,

Table *Electrophysiological data*

Case no.	*Pacing site*	*Cycle length*	*AP ERP*	*Atrium*		*Atrioventricular node*				*Upper limit echo zone*	*AP location*
						Fast		*Slow*			
				ERP	*FRP*	*ERP*	*FRP*	*ERP*	*FRP*		
1	RA	600	*	185	250	315	360	275	510	315	Left
	CS	600	*	215	255	310	360	260	490	355	
2	RA	400	*	205	268	307	358	<281	≤423	301	Left
	CS	400	*	210	259	312	343	279	405	323	
3	RA	800	429	235	302	391	471	345	607	399	Right
	CS	800	424	236	254	337	423	313	592	374	
4	RA	400	†	210	245	<245	≤285	NA	NA		3 APs
	RA	300	†	160	205	240	275	<205	≤310		
	CS	400	†	172	225	240	285	<225	≤320		
	CS	300	†	170	210	240	270	<210	≤315		
5	RA	500	†	220	250	310	345	<250	≤370		Right
	CS	500	†	255	290	<290	≤360	NA	NA		

AP, accessory pathway; CS, coronary sinus; ERP, effective refractory period; FRP, functional refractory period; NA, not achieved; RA, right atrium.

*Continuous block of conduction in anterograde direction at this cycle length.

†No accessory pathway present at postoperative study.

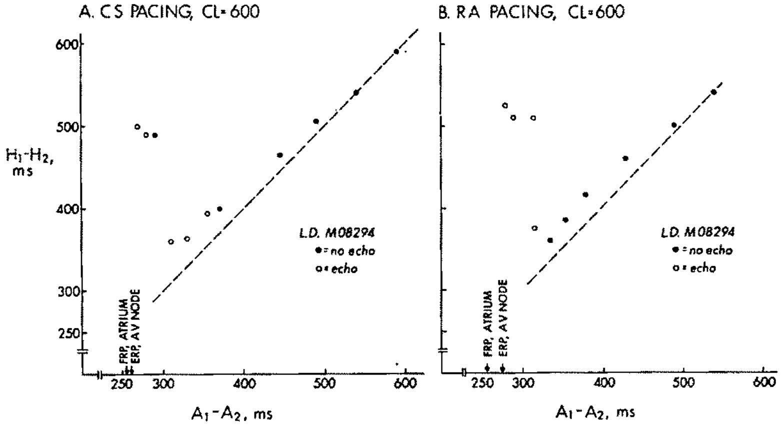

Fig. 1 *Case 1. Refractory period measurement using stimulation at cycle length 600 ms. (A) Coronary sinus pacing site. (B) Right atrial pacing site. At this cycle length there was continuous block of the accessory atrioventricular pathway in the anterograde direction. Therefore all driven impulses and all premature stimuli were conducted to the ventricle with normal QRS morphology. H_1–H_2 intervals could be measured at every coupling interval. The discontinuous curves are a result of dual atrioventricular nodal pathways. Open circles indicate H_1–H_2 intervals that initiated atrial echoes and tachycardia. Note that echoes and tachycardia were initiated by premature stimuli conducted over either the fast or slow atrioventricular pathways.*

and 351 ms were recorded. Only the H_1–H_2 interval of 409 ms initiated an atrial echo. This echo was recorded first in the lateral coronary sinus, confirming that it was initiated by conduction in the retrograde direction over the accessory pathway. All echoes were initiated by conduction in the retrograde direction over the accessory atrioventricular pathway, and the site of earliest atrial activation was always the lateral coronary sinus.

The tachycardia in cases 1 and 3 used only the slow atrioventricular nodal pathway for conduction in the anterograde direction. During tachycardia there was continuous block in the anterograde direction of the fast atrioventricular nodal pathway. Fig. 3 shows initiation of tachycardia in case 3. The AH interval recorded during the tachycardia varied between 250 ms and 330 ms. The RR intervals were similarly variable and the average interval was 491 ms (average heart rate = 122 beats/min).

In cases 4 and 5 the diagnosis of dual atrioventricular nodal pathways was made during an electro-

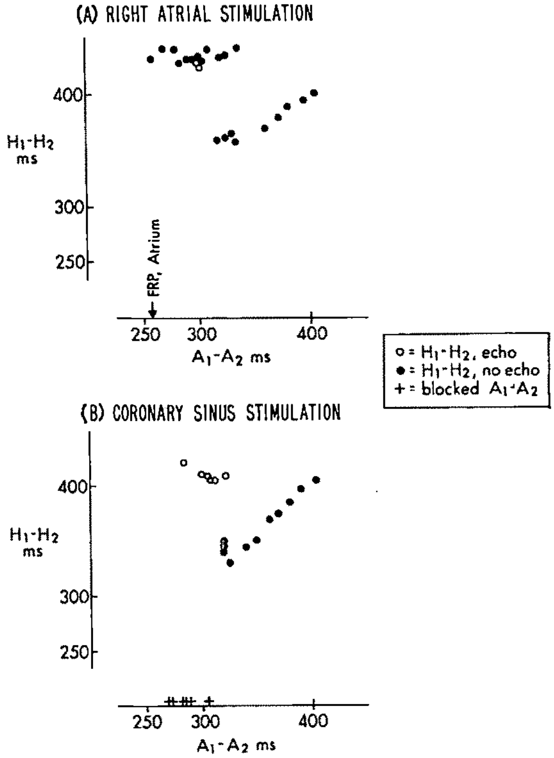

Fig. 2 *Case 2. (A) Refractory period measurement using stimulation of the right atrium at cycle length 400 ms. At this cycle length there was continuous block of the accessory atrioventricular pathway in the anterograde direction. All driven impulses and all premature stimuli were conducted to the ventricle with normal QRS morphology. H_1–H_2 intervals could be measured at every coupling interval. There is a discontinuity in the graph. Atrial echoes were generated only by premature stimuli that were conducted over the slow atrioventricular nodal pathway. Atrial refractoriness prevented the effective refractory period of the slow atrioventricular nodal pathway being determined exactly. (B) Refractory period measured using stimulation of the coronary sinus at cycle length 400 ms. There is again discontinuity in the graph. Only premature stimuli that were conducted over the slow atrioventricular nodal pathway initiated echoes. All atrial echoes were initiated in the lateral coronary sinus.*

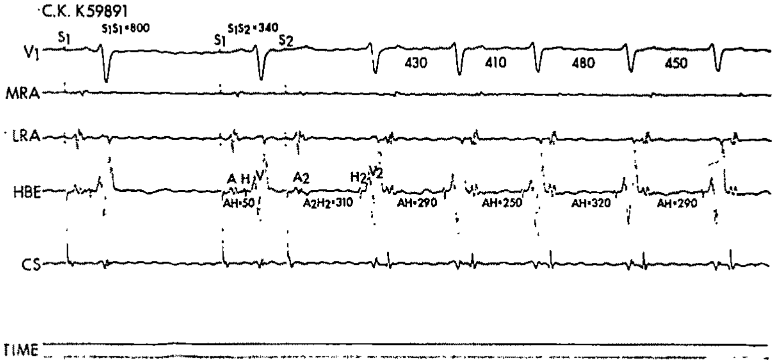

Fig. 3 *Reciprocating tachycardia (case 3). The fast atrioventricular nodal pathway was blocked during the tachycardia. AH intervals were variable and caused irregularity in the rhythm. The mean cycle length of the tachycardia was 491 ms (heart rate 122 beats/minute). CS, coronary sinus; HBE, His bundle electrogram; LRA, lateral right atrium; MRA, mid right atrium; V_1, ECG lead V1.*

physiology study performed several days after operative division of an accessory atrioventricular pathway. Data in the Table from cases 4 and 5 were recorded during the postoperative study. In the preoperative study of case 5 the effective refractory period of the accessory atrioventricular pathway in the anterograde direction was measured at the same cycle length used to measure refractory periods of the atrioventricular node in the postoperative study. During stimulation of the right atrium, the effective refractory period of the accessory pathway in the anterograde direction was 260 ms. During stimulation of the coronary sinus, the effective refractory period of the accessory pathway in the anterograde direction was 280 ms. Since these values were less than the effective refractory period of the fast atrioventricular nodal pathway measured using stimulation from corresponding sites, only slow atrioventricular nodal conduction times could be recorded in the preoperative study from either stimulation site.

Case 5 had two re-entrant tachycardias. One used the accessory atrioventricular pathway for conduction in the anterograde direction and one used the accessory atrioventricular pathway for conduction in the retrograde direction. This patient was advised that operative division of her accessory atrioventricular pathway would prevent only the re-entrant tachycardia which used the accessory atrioventricular pathway for conduction in the retrograde direction and that the other tachycardia might persist. She requested operation despite this reservation. At the time of the operation both tachycardias were observed. One tachycardia, as expected, used the atrioventricular node for conduction in the anterograde direction and an accessory atrioventricular pathway for conduction in the retrograde direction. The other tachycardia used both the atrioventricular node and the accessory atrioventricular pathway for conduction in the anterograde direction. Endocardial mapping of the right atrium was performed, and the origin of this latter tachycardia was found to be the anterior atrial septum. The accessory atrioventricular pathway was located in the right atrioventricular groove and was successfully divided. Dual atrioventricular nodal pathways were demonstrated by the extrastimulus technique during pacing of the right atrium in a postoperative study. No atrial echo or tachycardia was induced during the postoperative study, and the patient has had no spontaneous tachycardia in the postoperative period.

Refractory periods of the fast and slow atrioventricular nodal pathways were interesting because the effective refractory period and functional refractory period of both fast and slow atrioventricular nodal pathways measured using stimulation of the coronary sinus were equal to or less than the same refractory period measured using stimulation of the right atrium.

Discussion

This study shows the importance of basing criteria for diagnosing tachycardias on the behaviour of the tachycardia and not on the type of atrioventricular conduction present. For example, the presence of an initial delta wave on the QRS complex of an electrocardiogram recorded during sinus rhythm is a clinical marker for an abnormality of atrioventricular conduction in the anterograde direction in patients with the Wolff-Parkinson-White syndrome.[21] Dual atrioventricular nodal pathways are a clinical electrophysiological marker for another abnormality of atrioventricular conduction.[9] Paroxysmal supraventricular tachycardia can occur in patients with either abnormality.[21 22] In this study both abnormalities of atrioventricular conduction were present in five patients with paroxysmal supraventricular tachycardia. It is important to know the correct aetiology because paroxysmal supraventricular tachycardia caused by re-entry over an accessory pathway can be cured by operative division of the accessory pathway. In contrast, the operative treatment of paroxysmal supraventricular tachycardia resulting from re-entry within the atrioventricular node is division of the His bundle and implantation of a permanent pacemaker.

How often these abnormalities of atrioventricular conduction coexist is not known. Wellens has suggested that tachycardia caused by re-entry within the atrioventricular node should occur in patients with the Wolff-Parkinson-White syndrome with an incidence similar to that seen in the general population.[24] Simultaneous occurrence has been inferred from alternating cycle lengths recorded during tachycardia,[23] but well studied and documented cases are rare.[25] The prevalence of dual atrioventricular nodal pathways was 10 per cent in a large study of patients with conduction system disease[18] and this figure is consistent with the finding of dual atrioventricular nodal pathways in two of 19 (cases 4 and 5 of this report) consecutive patients with the Wolff-Parkinson-White syndrome studied after surgical correction of ventricular pre-excitation.[26]

In many patients with Wolff-Parkinson-White syndrome, a diagnosis of dual atrioventricular nodal pathways cannot be made.[6] Discontinuities in the curve of H_1–H_2 intervals generated by changing coupling intervals A_1–A_2 can only be shown in patients whose accessory atrioventricular pathway has an effective refractory period in the anterograde direction that exceeds that of the fast atrioventricular nodal pathway. Cases 4 and 5 are examples of this. In these patients dual atrioventricular nodal pathways were identified only after operative division of the accessory pathway.

We have seen one additional patient with the Wolff-Parkinson-White syndrome who was suspected of having dual atrioventricular nodal pathways because tachycardia with two distinct cycle lengths was observed. The sequence of retrograde activation of the atrium was identical during tachycardias with the two cycle lengths and began in the lateral left atrium; the only difference between the two tachycardias was the length of the AH interval. Sudden transitions from the slow to the fast tachycardia may occur both spontaneously and after programmed ventricular stimuli.[25 27]

Study by the atrial extrastimulus technique may suggest that a complex form of re-entrant tachycardia is present.[25] When refractory periods were measured with the extrastimulus technique during pacing of the atrium in cases 1 and 3, atrial echoes were initiated by premature stimuli that were conducted over both the fast and slow atrioventricular nodal pathways. In most descriptions of tachycardia caused by re-entry within the atrioventricular node, atrial echoes were initiated by premature stimuli which were conducted only over the slow atrioventricular nodal pathway.[7 8] Note that Fig. 2 is identical to figures made from data recorded in patients with tachycardia resulting from re-entry within the atrioventricular node and dual atrioventricular nodal pathways.[7 8] Endocardial mapping with a catheter in the coronary sinus was required to demonstrate the retrograde atrial activation from an accessory atrioventricular pathway.

Electrophysiological testing has been very useful in the evaluation of atrioventricular conduction, in determining the aetiology of arrhythmias, and in providing the basis for development of surgical techniques to manage arrhythmias that are refractory to control with drugs.[28] The results of this study clearly show the important distinction between abnormalities of atrioventricular conduction and the arrhythmias that accompany them. Criteria for the diagnosis of arrhythmias must be based on study of the arrhythmias themselves.

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Br Heart J 1980; **43:** 14–20

Study of cardiac rhythm in healthy newborn infants

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SUMMARY Twenty-four-hour electrocardiograms were recorded in the first 10 days of life on 134 healthy full-term infants with birthweights greater than 2·5 kg. The highest heart rate a minute, measured over nine beats, was 175±19 (SD). The lowest rates, measured over three, five, and nine beats were 82±12, 87±12, and 93±12, respectively. At their lowest rates 109 infants had sinus bradycardia and 25 had junctional escape rhythms. Thirty-three infants showed changes in P wave configuration with or without pronounced variation in PR interval. Atrial premature beats were present in 19 infants but only one had more than 12 per hour.

In a randomly selected subgroup of 71 infants sinus pauses were found in 51 (72%). Five (7%) had electrocardiographic patterns and rhythm disturbances that could not be differentiated from those previously described as complete sinuatrial exit block or sinus arrest, eight (11%) had patterns indistinguisable from 2:1 sinuatrial block, and 23 (32%) had patterns indistinguishable from sinuatrial Wenckebach block.

This study shows that normal infants have variations in heart rate and rhythm hitherto considered to be abnormal.

The range of heart rate and nature of heart rhythms are poorly documented in normal healthy infants. Twenty-four-hour recordings of the electrocardiogram provide an accurate means of measuring heart rate and rhythm over long periods. The technique does not seriously interfere with normal behaviour and therefore documentation of changes in rhythm and rate is possible during activities such as sleeping, feeding, or crying. This report describes the results of single 24-hour recordings of the electrocardiogram on 134 healthy full-term neonates who weighed over 2·5 kg at birth.

Patients and methods

Studies were made between birth and 10 days of age (the normal period of postnatal hospitalisation in this area) on 134 randomly selected infants born in West Dorset between January 1977 and June 1978. They were all healthy and recordings were performed in the maternity ward before discharge home. All infants studied had normal standard 12 lead electrocardiograms with a 10-second rhythm strip. They were studied under standard maternity ward environmental conditions and were fed and handled normally by their mothers during the recording period.

The recordings were made onto a Medilog cassette recorder* and the tapes were analysed for the presence of arrhythmias using a playback system* and arrhythmia detector*, by a trained technician. The Medilog recorder and analyser incorporated a synclock mechanism which, by providing and processing a reference time signal, ensured that possible variations in tape speed did not produce artefactual rhythm or rate disorders. Mothers were encouraged to handle their babies in the normal way while recordings were taken.

Heart rates during activity and rest were measured by a histogram module in the analyser*. Histograms of the distribution of different heart rates (as obtained by continuous measurement of all intervals) were made on 79 babies during approximately two hours each of activity and rest.

The maximum heart rates, measured by *direct* electrocardiographic analysis, over nine consecutive beats were recorded. The minimum rates found over three, five, and nine consecutive beats were also measured in this way and the heart rhythm at this time (whether sinus or junctional) was noted.

The number of premature beats over 24 hours was measured by counting them in four different, randomly selected, hours of recording and computing the total.

Received for publication 5 July 1979

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* Oxford Instrument Company.

Values for maximum and minimum heart rates were analysed and compared for ages 1 to 3 days and ages 4 to 10 days.

Seventy-one randomly selected recordings were analysed to determine if PP intervals were present which exceeded the previous PP interval by more than 50 per cent. If the QRS complex by which this interval was terminated was not preceded by a P wave the PQ interval was measured. When the PP or PQ interval exceeded the previous PP interval by more than 110 per cent this was classed as a pattern indistinguishable from complete sinuatrial block or sinus arrest (Fig. 1); intervals of between 90 and 110 per cent were classed as patterns of 2:1 sinuatrial block (Fig. 2) and intervals between 50 and 90 per cent were classed as sinus pauses (Fig. 3). This latter group was also assessed with respect to the pattern of PP intervals (a minimum of three) by which they were preceded.

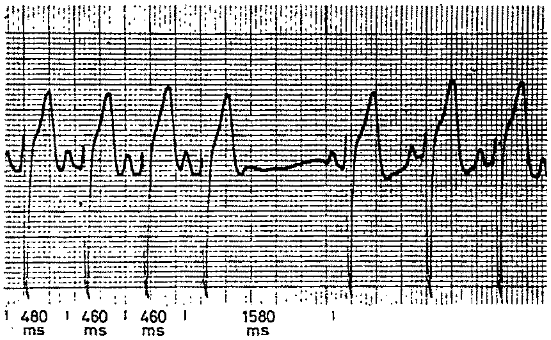

Fig. 1 *Extract from 24-hour electrocardiogram showing sudden lengthening of PP interval by more than 110 per cent of previous PP interval. This electrocardiographic pattern and rhythm disturbance cannot be distinguished from complete sinuatrial exit block or sinus arrest.*

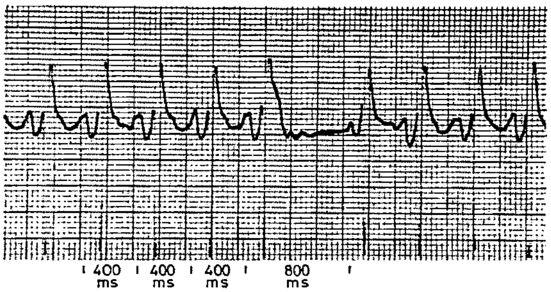

Fig. 2 *Extract from 24-hour electrocardiogram showing sudden lengthening of PP interval by between 90 and 110 per cent of previous PP interval. This electrocardiographic pattern and rhythm disturbance cannot be distinguished from 2:1 sinuatrial block.*

(1) Progressive increase in PP intervals.
(2) Regular PP intervals.
(3) Irregular PP intervals.
(4) A progressive decrease in PP intervals, that is a sinuatrial Wenckebach block pattern (Fig. 3c and 4).[1]

To differentiate sinuatrial Wenckebach block patterns from those of sinus arrhythmias we used the calculations of Schamroth and Dove[1] (see legend to Fig. 4) and also plotted the preceding PP intervals against their succeeding PP intervals (Fig. 5). The percentages used in our calculations were chosen empirically to try and match the labels and character of sinuatrial block pattern used by previous workers.

Results

All infants were predominantly in sinus rhythm and showed a minimal, continuous irregularity of rate previously termed phasic variation.[2]

The distribution of heart rates (derived from RR intervals) at rest and during activity measured by the histogram module in the analyser showed a maximum heart rate of 250/minute and a minimum rate of 85/minute. Direct electrocardiographic analysis of these higher and lower heart rates showed them to be spuriously high because of the interpretation of movement artefact and large T waves as R waves.

The histogram of the highest rate achieved over 24 hours measured by direct electrocardiographic analysis over nine beats did not differ significantly from a curve of normal distribution* with a mean rate of 175 ±19 (SD). The highest heart rate found was 225/minute. The histograms of the lowest rates measured by direct electrocardiographic analysis over three, five, and nine beats duration over 24 hours also did not differ from a normal distribution.* The mean lowest heart rate when measured over three beats was 82/minute, over five beats was 87/minute, and over nine beats was 93/minute. The standard deviation in each case was 12.

Of 134 infants, 109 at their lowest heart rates had sinus bradycardia and 25 had junctional escape rhythms. All infants showed sudden short episodes of bradycardia (Fig. 6).

The three infants with the lowest heart rates are described in more detail. One aged 8 days had an episode of bradycardia of 10 beats duration when the rate fell to 42/minute. This began with two atrial premature beats, was followed by a sinus pause of 1·8 seconds, and continued with a slow junctional escape rhythm (Fig. 7). Four other episodes of bradycardia occurred during the

*Confirmed by Kolomogorov-Smirnov test.[3]

recording. The second infant aged 2 days showed an episode of 14 beats duration where the rate fell to 59/minute. His only sib had previously died from the sudden infant death syndrome. The third infant was 4 hours old when the 24-hour recording was started. Subsequent analysis showed seven episodes of bradycardia of between 59 and 63/minute and of between 12 and 18 beats duration. The first three episodes coincided with cyanotic attacks, observed by the nursing staff and treated by stimulation and oronasal suction. No cause was found for these attacks. Though there were four further episodes of bradycardia during the night no cyanotic attacks were detected.

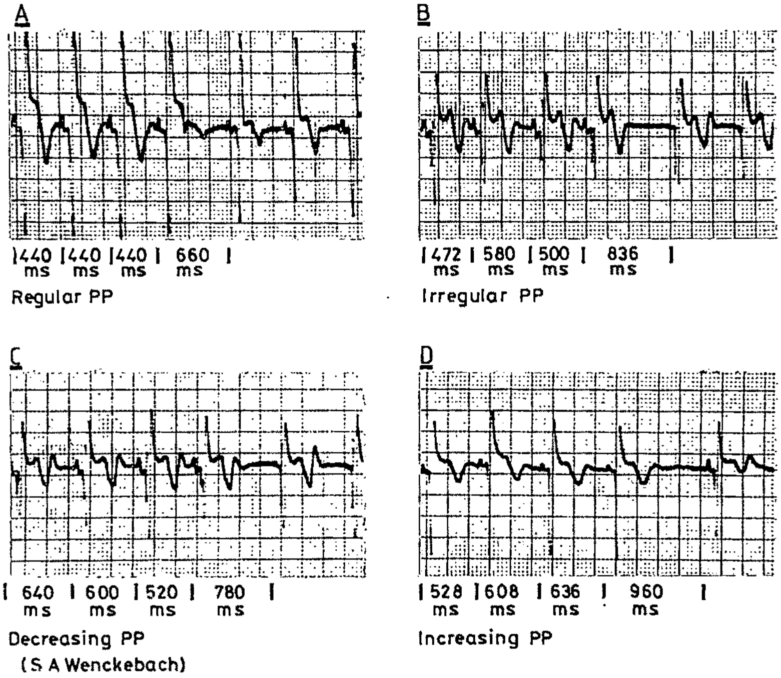

Fig. 3 *Four extracts from 24-hour electrocardiograms on different infants showing sinus pauses. In each case there is sudden lengthening of PP or PQ intervals exceeding previous PP intervals by 50 to 90 per cent. In* (A) *preceding PP intervals are regular; in* (B) *they are irregular, and in* (D) *they are increasing before the pause. In* (C) *there is progressive decrease in PP intervals before the pause and this electrocardiographic pattern cannot be distinguished from sinuatrial Wenckebach block.*

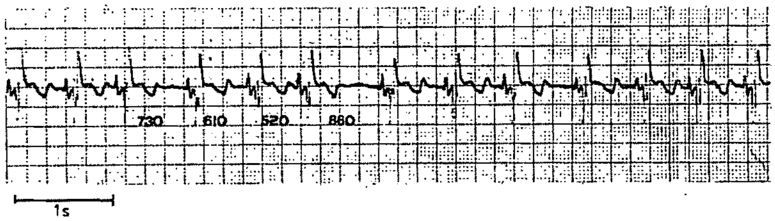

Fig. 4 *Twenty-four-hour recording showing a series of sinus pauses. Labelled central pause is preceded by progressive reduction in PP intervals. Using calculations of Schamroth and Dove*[1] *sinus cycle*

$$= 610 + 520 + 860 = \frac{1990}{3+1} = 498$$

P1 – P2 increment = 610 – 498 = 112
P2 – P3 increment = 520 – 498 = 22
Total increment = 134
860 + 134 = 994 which is approximately twice sinus cycle of 498.
Sinus extrasystole before pause is unlikely because pause exceeds sinus cycle by 362 ms.

Table 1 *Analysis of extrasystoles from single 24-hour electrocardiograph recordings on 134 infants*

No. of extrasystoles in 24 hours	*No. of infants*
1 to 12	12
12 to 24	1
24 to 48	2
96 to 120	2
144 to 168	1
480 to 600	1

Changes in P wave configuration and PR interval variation occurred in 33 (25%) infants (Fig. 8).

Nineteen infants (14%) had atrial premature beats but only one had more than 12 per hour (Table 1).

There was no significant difference between the two age groups, 1 to 3 days and 4 to 10 days, for measurements of maximum and minimum heart rates (Table 2).

Of the subgroup of 71 infants, five (7%) had electrocardiographic patterns, ie sinus pauses, that could not be differentiated from those described in all the other articles studied as complete sinuatrial exit block or sinus arrest (Fig. 1). Eight infants (11%) had sinus pauses indistinguishable from 2:1 sinuatrial block (Fig. 2).

The longest interval between an escape beat and the previous sinus beat was 1·8 seconds (Fig. 6).

Sinus pauses representing increases in PP intervals of 50 to 90 per cent were found in 51 subjects (72%) with preceding PP interval patterns as follows (Fig. 3). (1) Progressive increase 23 subjects (32%); (2) regular PP intervals 14 subjects (20%); (3) irregular PP intervals 35 subjects (50%); and (4) progressive decrease (sinuatrial Wenckebach pattern) 23 subjects (32%) (Fig. 3c and 4). The calculations of sinus cycle increments (Fig. 4) and graphs of succeeding PP interval measurements (Fig. 5) supported the presence of Wenckebach conduction rather than sinus arrhythmia in all 23 subjects.

Some subjects showed more than one pattern.

Discussion

The range of heart rates found in these healthy neonates is wider than previously reported on standard electrocardiograms.[4] The mean lowest rate measured by direct electrocardiographic analysis over nine beats was 83/minute, with a standard deviation of 12. Heart rates as low as 60/minute for short periods of time are therefore to be expected in the normal neonatal population. Though 25 per cent of infants at their lowest rates had short episodes of junctional escape rhythm, prolonged periods of junctional rhythm with retrograde P wave activity were not found in our study. Episodes of sudden bradycardia are a distinct feature of the cardiac rhythm at this age and have previously been reported in association with sudden deep breaths, hiccoughs, bowel movements, and vomiting.[2 5 6] We are at present evaluating the relation of apnoea and other physiological functions to these episodes.[7]

Electrocardiographic patterns that we could not differentiate, without invasive electrophysiological tests, from those described in previous studies as complete, 2:1, Wenckebach sinuatrial block, or sinus arrest were found in 50 per cent of infants studied. They were also found in our recently completed investigation of 24-hour electrocardiograms on 92 randomly selected healthy children aged 7 to 11 years.[8] These electrocardiographic patterns have often been interpreted as disorders of sinus node function and clinical events such as faints, 'funny turns', or blackouts ascribed to this cause when these electrocardiographic patterns are

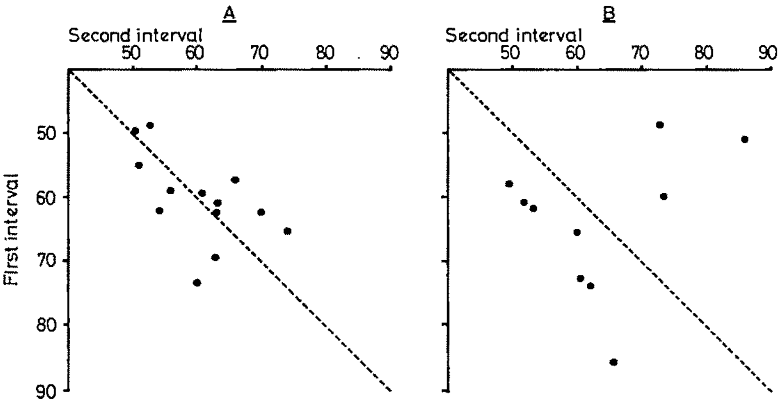

Fig. 5 *A plot of PP intervals on the Y axis against succeeding PP intervals on X axis. The line shows position of PP intervals of equal duration.* (A) *Pattern of sinus arrhythmia.* (B) *Pattern of sinuatrial Wenckebach block.*

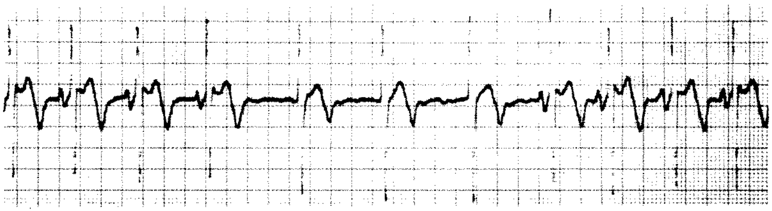

Fig. 6 *24-hour electrocardiogram showing sudden short-lived episode of bradycardia at 72/min (as measured over five beats) with a junctional escape rhythm.*

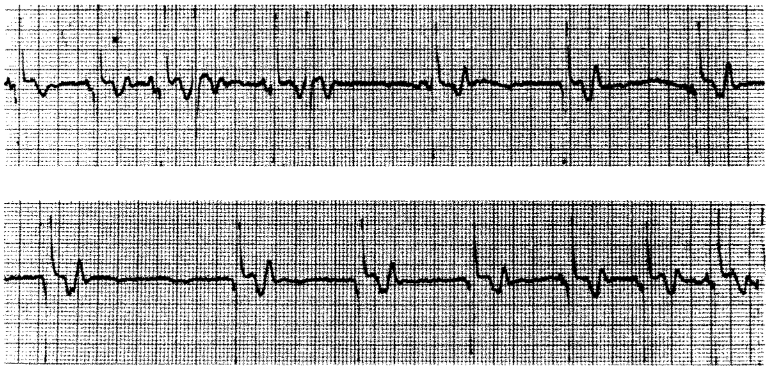

Fig. 7 *24-hour electrocardiogram showing sudden bradycardia of approximately 12 seconds duration where heart rate falls to 42/min (as measured over nine beats). Bradycardia begins with two atrial premature beats and is followed by sinus pause and slow junctional escape rhythm. First escape beat is preceded by P wave but is probably junctional in origin. This episode of bradycardia includes an asystolic pause of 1·8 seconds.*

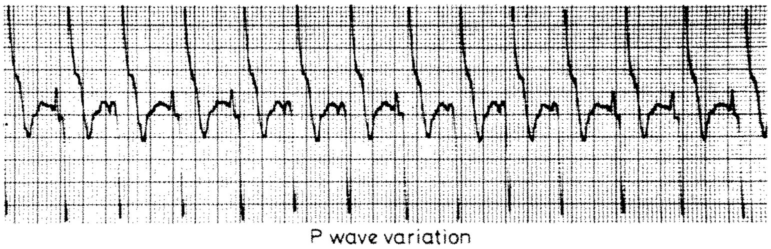

Fig. 8 *24-hour electrocardiogram showing variation in P wave configuration and duration of PR interval, without changes in heart rate.*

found on standard or 24-hour electrocardiograms.[9] [10] Moreover, the management of the 'tachycardia—bradycardia' syndrome is often said to be complicated by inappropriate bradycardias when suppressant therapy is given for the tachycardia.[9] The degree and patterns of bradycardia regarded as inappropriate must also take normal data into consideration and not lead to the unnecessary withholding of therapy.

In the assessment of surgical procedures for congenital heart disease[11–13] intermittent junctional escape rhythms and electrocardiographic patterns similar to those described above have been, in all cases, interpreted as disorders of sinus node function and assumed to be acquired arrhythmias. This supposition is probably incorrect.

As electrocardiographic patterns indistinguishable from sinuatrial block and junctional rhythm are now known to occur frequently in healthy neonates and children, other criteria, on standard or 24-hour electrocardiograms, are necessary to determine if there is an abnormality of sinus node function. One possibility is to measure the time taken for an escape rhythm to be initiated after a sinus pause. The longest escape interval found in healthy neonates studied here was 1·8 seconds. In a recent report of an example of the sick sinus syndrome in an infant with sinuatrial and atrioventricular conduction disturbance, proven by electrophysiological studies, episodes of asystole exceeding four seconds were described.[14]

In our opinion all the premature beats found in this investigation were supraventricular. To arrive at this conclusion we examined the width of the QRS complex and the length of the compensatory pause, and looked for preceding P waves. We have already reported that 18 of 2030 (0·9%) newborn infants screened by a standard electrocardiogram with a 10-second rhythm strip had premature beats, many of which were ventricular in origin.[15] [16] Twenty-four-hour recordings showed episodes of ventricular or supraventricular tachycardias in

Table 2 *Comparison of lowest and highest rates over 24 hours in age group 1 to 3 days and age group 4 to 10 days*

	Highest rate/minute (measured over 9 beats)				*Lowest rate/minute (measured over 3 beats)*				*Lowest rate/minute (measured over 9 beats)*			
Age (d)	*Min.*	*Max.*	*Mean*	*SD*	*Min.*	*Max.*	*Mean*	*SD*	*Min.*	*Max.*	*Mean*	*SD*
1–3	120	220	173	19	53	105	81	11	59	119	93	12
4–10	140	205	179	16	36	110	82	14	42	120	94	13
P value	< 0·10				Not significant				Not significant			

Table 3 *Comparison of reports on long-term electrocardiographic monitoring in the neonate*

	Southall et al.[7]	*Välimäki*[18]	*Välimäki and Tarlo*[19]	*Morgan and Guntheroth*[17]
Duration of recording (hr)	24	36	30	5
Number studied	134	50	68	50
Age at recording (d)	1–10	1–2	1–2	1–7
Maximum heart rate per min	220	260	260	170
Minimum heart rate per min	42	86	80	75
Junctional escape rhythms (%)	19	10	13	—
P wave and PR interval variation (%)	25	20	15	—
Premature beats (%)	14	8	9	2 plus 'a few'

five of this latter group. Premature beats, frequent enough to be detected on standard electrocardiograms, are therefore more likely to be associated with tachyarrhythmias than occasional premature beats found only on 24-hour electrocardiographic recordings. The latter are likely to be a normal feature of the newborn heart rhythm.

In Table 3 the findings of our study are compared with those of three other reports describing long-term electrocardiographic monitoring of healthy full-term infants.[17–19] The maximum and minimum heart rates found by Välimäki[18, 19] are higher than those found by the direct electrocardiographic analysis method used in our study. Their technique of measuring rate was, however, similar to the automatic histogram module of our 'Oxford' analyser. We have shown that movement artefacts and large T waves are often interpreted as extra QRS complexes by this automatic histogram module, thus giving spuriously high heart rates. This could explain the higher results in their study. The shorter time of recording used by Morgan and Guntheroth[17] may explain the absence of junctional escape rhythms or the absence of P wave and PR interval variation in their study.

Twenty-four-hour recordings have shown that electrocardiographic rhythm patterns previously described as representing disorders of sinus node function occur in the healthy neonate. We have also found differences between the values of highest and lowest heart rates measured in this study and those previously reported on long-term electrocardiographic recordings. The interpretation of heart rhythm and rate in clinical situations must take normal data into consideration.

Dr Southall has a grant from the Board of Governors of the Brompton Hospital, and Jean Richards from the Foundation for the Study of Infant Death. The project was supported by grants from the British Heart Foundation and the Wessex Regional Health Authority. Generous donations were also given by the League of Friends of Dorchester and Weymouth Hospitals, the Weymouth Round Table, Weymouth Lions, and Weymouth Auxiliary League of the Licensed Trade.

The Oxford Instrument Company gave invaluable support to this work.

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Cardiac rhythm and conduction before and after Mustard's operation for complete transposition of the great arteries

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SUMMARY Between 1973 and 1978, 120 patients with transposition of the great arteries had a modification of Mustard's operation designed to avoid damage to the sinus and atrioventricular nodes. Of these, 88 had an atrial baffle alone from which nine hospital and four late deaths occurred (total mortality 14·8%); 32 had additional closure of ventricular septal defect and/or relief of left ventricular outflow tract obstruction from which six hospital and three late deaths occurred (28%).

On the standard electrocardiogram, 101 of 105 patients (96%) discharged from hospital were in sinus rhythm, but of the four patients with arrhythmias two had conduction abnormalities before operation. A further two patients with complex procedures had acquired bifascicular block. Twenty-four-hour electrocardiograms in 19 patients who had both pre- and postoperative recordings showed acquired arrhythmias in one of 13 who had simple Mustard's operation and in two of six who had additional procedures. Of a further 39 patients who had only postoperative 24-hour recordings, three of 30 with a simple operation and three of nine with additional surgical procedures had arrhythmias that were thought to be acquired.

Rhythm patterns and rates previously considered to be surgically acquired were found before operation on 24-hour electrocardiograms in patients with complete transposition and have now been reported to occur in normal infants and children. There is thus no evidence to support the view that such episodes with the electrocardiographic patterns of Wenckebach, 2:1 or complete sinuatrial block, atrial premature beats of less than 12 per hour, or intermittent junctional escape rhythms represent acquired cardiac arrhythmias.

Seven of the 22 deaths occurred after leaving hospital and included five which were sudden and unexpected, no adequate cause being found at necropsy. Four of these had conduction disorders or arrhythmias on standard and 24-hour electrocardiograms including three with complex procedures.

Our results indicate that a modified Mustard's operation may reduce the frequency of surgically acquired arrhythmias.

Arrhythmias occurring after interatrial repair, Mustard's operation[1] of complete transposition of the great arteries (concordant atrioventricular and discordant ventriculoarterial connections) have been widely reported.[2–4] Standard 12 lead electrocardiograms have shown persistent arrhythmias in one-tenth to two-thirds of patients.[3–5] Saalouke *et al.*[6] showed abnormal sinus node function in 63 per cent and abnormal atrial effective refractory periods in 33 per cent of patients studied by intracardiac electrophysiological techniques. Saalouke *et al.*[6] and Goodwin *et al.*[7] also detected arrhythmias in 100 per cent of patients using 24-hour Holter monitoring.

Arrhythmias found after Mustard's operation have been variously explained by damage to the sinus node or its artery,[3 5 8] to the atrioventricular node,[4] to the postulated 'specialised internodal

Received for publication 5 July 1979

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pathways',[9] or to a combination of these.

At the Brompton Hospital one surgeon has used a standardised technique specifically designed to avoid nodal damage, but making no attempt to preserve the postulated specialised internodal pathways. A review of the postoperative standard electrocardiograms from patients having this modified operation revealed fewer arrhythmias than did studies reported by other workers. In order to evaluate this further, we have examined pre- and postoperative standard electrocardiograms and both pre- and postoperative 24-hour electrocardiograms whenever possible on patients undergoing Mustard's operation. The results of both the standard and 24-hour recordings form the subject of this report.

Patients, surgical techniques, and methods

One hundred and twenty patients aged between 2 weeks and 8 years were operated upon at the Brompton Hospital by one surgeon. Of these, 96 patients had undergone a previous balloon atrial septostomy, three patients had had atrial septectomies, and 21 patients had had neither procedure. Eighty-eight patients had placement of an atrial baffle alone (simple Mustard's operation). In four this was a palliative procedure, a ventricular septal defect being left open because of the presence of pulmonary vascular obstructive disease. There were 13 deaths in this group (14·8% mortality), four of whom had pulmonary vascular disease. Of these deaths, nine were perioperative and four were late deaths after discharge from hospital. Thirty-two patients had additional closure of ventricular septal defect and/or relief of left ventricular outflow tract obstruction (complex Mustard's operation), and nine died (six early and three late deaths, total mortality 28%). Standard 12 lead electrocardiograms were recorded before operation in all patients from both groups and after operation on the 105 patients who left hospital. Follow-up recordings were made on 69 patients at three months, 63 patients at six months, 51 at one year, 41 at two years, and 28 at three to four years after operation. Twenty-four-hour electrocardiograph tape recordings were performed on a total of 58 patients; 19 had both pre- and postoperative recordings and included 13 with simple and six with complex transposition. Twenty-four-hour recordings were made at times ranging from two weeks to four years after the operation and more than one recording was made on the majority of subjects. These patients were unselected and their inclusion in this part of the study depended upon the availability of recorders at the time of hospital attendances or on the frequency of outpatient attendances. Eight patients were discharged to the care of doctors in other countries and their postoperative electrocardiograms are not available. To the best of our knowledge none of this latter group of patients has died.

In the interpretation of the 24-hour electrocardiographic data we have taken account of normal values obtained from the 24-hour electrocardiographic study of 134 healthy neonates,[10] and 92 healthy schoolchildren aged between 7 and 12 years, without congenital heart disease.[11] Atrial premature beats of less than 12 per hour have been shown to be frequently present in infancy[10 12 13] and were therefore not considered in this report to be abnormal. Electrocardiographic patterns indistinguishable from Wenckebach sinuatrial block, 2:1 sinuatrial block, or complete sinuatrial block and intermittent junctional escape rhythms have also been described as 'normal' findings on 24-hour electrocardiograms in healthy infants and schoolchildren.[10 11] Nevertheless, to allow comparison with other reports their occurrence is documented in the results section.

RECORDING AND ANALYSIS

Twenty-four-hour recordings were performed on a Medilog cassette recorder* using two electrodes (Simonsen and Weel, silver chloride electrode type 810) one placed high over the right sternal border and the other in the V6 position in the left axilla. The 24-hour tapes were analysed directly by a trained technician using a playback system and arrhythmia detector.* The recorder and analyser incorporated a synclock system which, by providing a reference time signal, ensured that possible variations in tape speed did not produce artefactual measurements of rhythm or rate.

SURGICAL TECHNIQUE (Fig. 1)

A constant technique was employed in each patient for cannulation and insertion of the atrial baffle. Cardiopulmonary bypass with moderate or profound hypothermia with circulatory arrest was used in these patients. The heart was approached through a median sternotomy and the ascending aorta cannulated. The superior vena cava was cannulated through the right atrial appendage and the inferior vena cava at its junction with the right atrium. Where circulatory arrest was used a single venous cannula was placed into the right atrium through the appendage. The encircling snare for the superior vena cava was always placed well cephalad to its junction with the atrium. The right atrial incision passed from the area of the atrial appendage coronally towards the junction of the upper and lower right pulmonary veins and across the crista

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*Oxford Instrument Company.

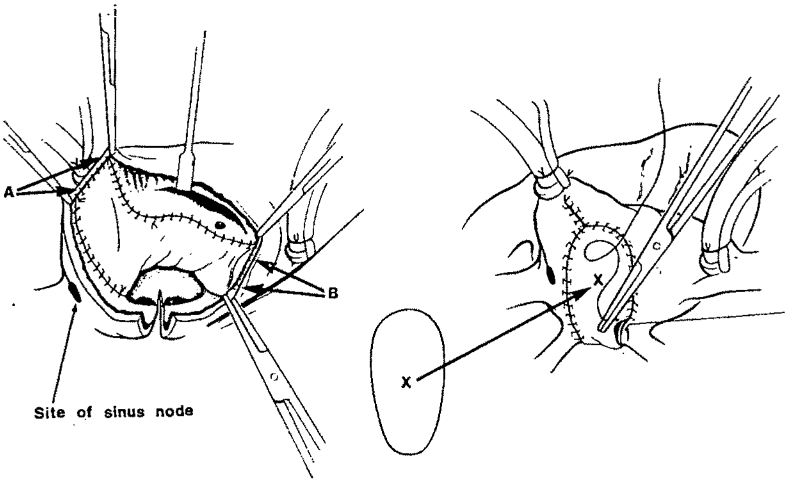

Fig. 1 *Intra-operative drawing for the interatrial baffle operation for correction of transposition of the great arteries. The incision in the right atrium is coronal and extends onto the back wall of the left atrium.* (A) *points to the attachment of the baffle in the region of the superior vena caval orifice. It has been sutured to the cut edge of the atriotomy.* (B) *points to the attachment of the baffle in the region of the inferior vena caval orifice, once again to the cut edge of the atriotomy.* (X) *An enlarging patch is placed in the lower part of the atriotomy thereby increasing the size of the pulmonary venous atrium.*

terminalis. The interatrial septum was widely excised particularly in the region of the superior limbus of the fossa ovalis. The interatrial baffle of thin Dacron cloth was trouser-shaped after the design of G. Brom (1975, personal communication). The pulmonary venous atrium was enlarged by extending the incision between the upper and lower right pulmonary veins round on to the posterior left atrial wall and inserting a patch of woven Dacron or autologous material. The coronary sinus was left intact draining to the new pulmonary venous atrium. The suture lines for the baffle attachment were placed superior to the coronary sinus; the periphery of the attachment of the baffle was placed well away from the ostia of the superior and inferior vena cavae and incorporated the cut edge of the atriotomy. Continuous sutures were used throughout. Closure of the ventricular septal defect in the majority of cases was effected through the tricuspid valve. Some patients, particularly those with an infundibular septal or immediately subaortic defect required a right ventriculotomy placed high in the infundibulum. Left ventricular to pulmonary artery valved conduits were used to relieve severe cases of subvalvar pulmonary stenosis in five patients.

Results

(A) STANDARD ELECTROCARDIOGRAPHIC DATA (Table 1)

Before operation, 119 of 120 patients were found to be in sinus rhythm on a standard 12 lead electrocardiogram.

Of the 105 (96%) postoperative patients discharged from hospital, 101 remained in sinus rhythm with normal atrioventricular conduction on the standard electrocardiogram. Of the four patients not in sinus rhythm, one, who was not on treatment,

Table 1 *Arrhythmias or conduction disorders on standard electrocardiograms found in six of 105 patients discharged from hospital after operation*

		Electrocardiogram		
Case no.	*Operation*	*Preoperative*	*Postoperative*	*Outcome*
1	Simple	1° AV block PR 0·24 s	Complete AV block QRS 0·06 s	Late death
2	Simple	Complete AV block	Complete AV block QRS 0·08 s	Well
3	Complex (previous septectomy, transatrial VSD repair)	Normal conduction	Atrial fibrillation	Well
4	Complex	Normal conduction	Complete AV block QRS 0·08 s	Pacemaker
5	Complex (transatrial VSD repair)	Normal conduction	RBBB + LAD (−90°)	Late death
6	Complex	Normal conduction	RBBB + LAD (−135°)	Late death

AV, atrioventricular; LAD, left axis deviation; RBBB, right bundle-branch block.

had first degree atrioventricular conduction delay preoperatively, with a PR interval of 0·24 s. After operation this patient had complete atrioventricular block with a QRS duration of 0·06 s, and died suddenly five months after operation. Another patient developed complete heart block (QRS 0·08 s) during preoperative cardiac catheterisation. Despite persistence of this rhythm postoperatively, the patient has remained well (follow-up for four years, no pacemaker). Both these patients had a Mustard's operation alone.

Two others who had complex procedures developed arrhythmias—one atrial fibrillation and the other complete atrioventricular block (QRS 0·08 s); the latter required permanent pacemaker insertion because of Adams-Stokes attacks. Two further patients undergoing complex procedures were in sinus rhythm after operation but had bifascicular block pattern on the electrocardiogram (complete right bundle-branch block and axes of −90° and −135°, respectively); both were sudden late deaths.

(B) 24-HOUR ELECTROCARDIOGRAPHIC DATA

(1) *Pre- and postoperative data* (Table 2 and 3)

Three of 19 patients (16%) had abnormalities of rhythm after operation, which were not present before; one out of 13 had simple Mustard's operation and two out of six had had a complex procedure. In the one patient with Mustard's operation alone multiple (60 per hour) atrial premature beats were present. Of the two patients undergoing complex procedures, one had very frequent atrial premature beats (700 per hour) and the other had bouts of probable ventricular tachycardia (rate 280 per minute) (Fig. 2). Heart rates between 40 and 50 per minute, junctional escape rhythms, electrocardiographic patterns of 2:1 Wenckebach and complete sinuatrial block (Fig. 3), and atrial premature beats of less than 12 per hour were

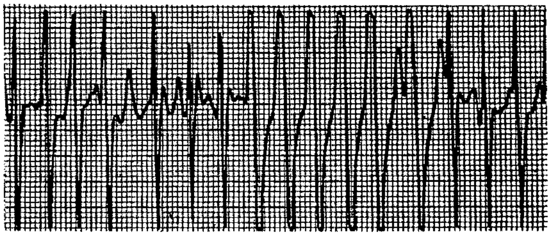

Fig. 2 *24-hour electrocardiogram showing a probable ventricular tachycardia at 280/minute. The sixth beat represents either capture or fusion; there is no constant relation between the QRS during the tachycardia and the P waves; the QRS is broad (0·12 seconds) and ventricular premature beats were found in other parts of the recording.*

Table 2 *Pre- and postoperative 24-hour electrocardiograph results on 19 patients who had Mustard's operation*

Subject	*Age at operation*	*Preoperative*		*Postoperative*	
		Rhythm	*Lowest rate*	*Rhythm*	*Lowest rate*
Simple operations					
7	10 days	SAW, J 2:1 SAB APBs (< 12/h)	$\geqslant$50	SAW, J 2:1 SAB	$\geqslant$50
8	21 days	Sinus	$\geqslant$50	Sinus	$\geqslant$50
9	3 months	APBs (< 12/h)	$\geqslant$50	APBs (< 12/h)	$\geqslant$50
10	8 months	2:1 SAB	$\geqslant$50	Sinus	$\geqslant$50
11	10 months	Complete SAB SAW, J (Fig. 3)	$\geqslant$50	APBs (< 12/h)	$\geqslant$50
12	11 months	SAW	$\geqslant$50	SAW	$\geqslant$50
13	15 months	SAW, J 2:1 SAB	45–49	SAW, J 2:1 SAB (Fig. 5, 6, 7)	35–39
14	16 months	SAW	$\geqslant$50	SAW, J APBs (< 12/h)	$\geqslant$50
15	18 months	Sinus	$\geqslant$50	Sinus	$\geqslant$50
16	18 months	APBs (< 12/h)	$\geqslant$50	J	$\geqslant$50
17	2 years	Sinus	$\geqslant$50	Sinus	$\geqslant$50
18	2 years	SAW, J	40–44	SAW, J	$\geqslant$50
19	7 years	J	$\geqslant$50	APBs (60/h)	$\geqslant$50*
Complex operations					
20	6 months	APBs (< 12/h)	$\geqslant$50	APBs (< 12/h)	$\geqslant$50
21	9 months	Sinus	$\geqslant$50	SAW, J	$\geqslant$50
22	4 years	Sinus	$\geqslant$50	VT (300/min) (Fig. 2)	$\geqslant$50*
23	5 years	SAW, J	$\geqslant$50	Sinus	$\geqslant$50
24	6 years	SAW	$\geqslant$50	SAW	45–49
25	7 years	SAW, J	$\geqslant$50	SAW, J APBs (700/min)	$\geqslant$50*

APB, atrial premature beat; J, intermittent junctional escape rhythm; *, considered to be 'abnormal', acquired arrhythmias; SAB, ECG patterns indistinguishable from sinuatrial block or sinus arrest; SAW, sinuatrial Wenckebach block; VT, ventricular tachycardia present in the 19 patients as frequently before as after the operation (Table 2) and were not classified as 'abnormal' cardiac arrhythmias. One child in whom the rate was 45 to 50 per minute before operation had a rate of 35 to 40 per minute one year after operation.

(2) *Additional postoperative data*

(a) Simple Mustard's operation (Table 4). Of 30 patients studied, three had abnormal arrhythmias (10%). These consisted of episodes of supraventricular tachycardia in two patients with additional atrioventricular block in one case (Fig. 4) and multiple atrial premature beats in the third. A further patient who had intermittent complete atrioventricular block before operation was shown to have a similar rhythm after operation with no episodes of asystole. Twenty-two had intermittent junctional escape rhythms, 23 had

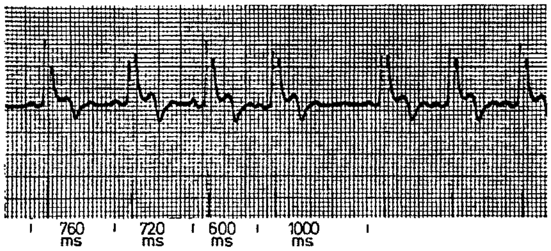

Fig. 5 *24-hour electrocardiogram showing a pattern indistinguishable from sinuatrial Wenckebach block (second degree). There is a progressive diminution of PP intervals before a pause which is between 50 and 90 per cent longer than the previous PP interval. The beat immediately preceding the pause is unlikely to have been an atrial extrasystole because in the illustration the coupling interval is long and the pattern was repeatedly seen with more obviously normal P waves at other times during the recording. Similar rhythm patterns were found on 24-hour electrocardiograms of normal infants and children.*

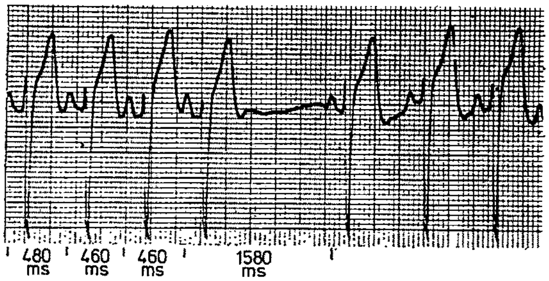

Fig. 3 *24-hour electrocardiogram showing an electrocardiographic pattern indistinguishable from complete (third degree) sinuatrial block or sinus arrest. There is a sudden lengthening of PP interval by more than twice the preceding PP intervals. The escape beat is probably sinus in origin. Similar rhythm patterns are found on 24-hour electrocardiograms of normal infants and children.*

Table 3 *Comparison of pre- and postoperative 24-hour electrocardiographic data on 19 subjects*

	Number of subjects	
	Before operation	*After operation*
Sinus rhythm	5	5
Intermittent junctional escape rhythm	7	7
Electrocardiographic patterns of sinuatrial block	10	8
APBs < 12/h	4	4
APBs > 12/h*	0	2
Ventricular tachycardia*	0	1
Lowest heart rate >50	17	17
Lowest heart rate 45–49	1	1
Lowest heart rate 40–44	1	0
Lowest heart rate 35–39	0	1

*, considered to be 'abnormal' arrhythmias.
APB, atrial premature beat.

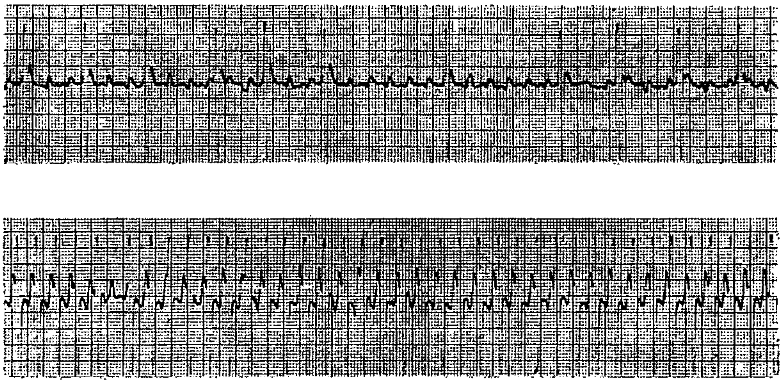

Fig. 4 *24-hour electrocardiogram showing a supraventricular tachycardia of 300/minute* (upper and lower panels), *with episodes of atrioventricular block* (upper panel). *This child was not receiving digoxin.*

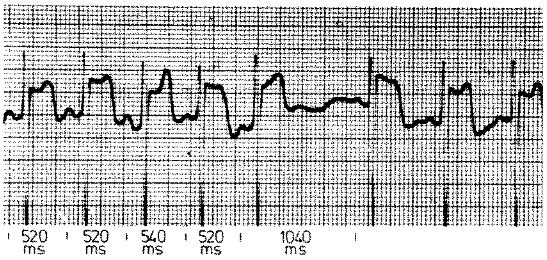

Fig. 6 *24-hour electrocardiogram showing a pattern indistinguishable from 2:1 (second degree) sinuatrial block. Similar rhythm patterns are found on 24-hour electrocardiograms of normal infants and children.*

Table 4 *Additional postoperative 24-hour electrocardiographic results on 30 patients who had simple Mustard's operation*

No. of patients	*Postoperative* *Rhythm*	*Lowest rate*	*Age at 24-hour recording*
4	Continuous sinus rhythm	50	12, 18, 28, 30 months
1	J	50	28 months
3	SAW	50	13, 22, 31 months
1	SAW	45–49	3 years
7	SAW, J	50	1½, 1½, 2, 5, 6, 6. 7 years
4	SAW, J	45–49	3, 4, 7, 8 years
1	SAW, J	40–44	4 years
1	SAW, J	35–39	3 years
1	2:1 SAB	50	3 years
2	SAW, J APBs (< 12/h)	50	3, 7 years
1	SAW, J APBs (< 12/h)	35–39	4 years
1	SVT 260/min plus		7 years*
1	SVT SAW, J	50	3 years*
1	CAVB	45–49	4 years*†
1	APBs (> 12/h) SAW, J	50	18 months*

*, considered to be abnormal arrhythmias; †, also present on standard ECG pre- and postoperatively; AV, atrioventricular; APB, atrial premature beats; CAVB, complete atrioventricular block; J, intermittent junctional escape rhythm; SAB, ECG pattern indistinguishable from sinuatrial block; SAW, ECG pattern indistinguishable from sinuatrial Wenckebach block; SVT, supraventricular tachycardia.

electrocardiographic patterns of sinuatrial Wenckebach block (Fig. 5), one had electrocardiographic patterns of 2:1 sinuatrial block (Fig. 6), eight had rates between 40 and 50 per minute, and two had rates between 35 and 40 per minute (Fig. 7).

(b) Mustard's operation complicated by other procedures (Table 5). Of the nine patients studied, three had acquired arrhythmias (33%); multiple ventricular premature beats with couplets in one (Fig. 8), multiple atrial premature beats (30 per hour) in another, and bouts of supraventricular trachycardia in the third. In addition, six had intermittent junctional escape rhythms, six had electrocardiographic patterns indistinguishable from sinuatrial Wenkebach block, one had atrial premature beats of less than 12 per hour, three had rates between 45 and 50 per minute, and one had a rate of between 35 and 40 per minute.

In summary, of a total of 43 patients (13 + 30) who had a simple Mustard's operation, four had what could be considered abnormal arrhythmias (9%) on 24-hour recordings, and of the 15 patients (six plus nine) studied who had additional procedures five had abnormal arrhythmias (33%).

(3) *Artefact problems*

A common problem when analysing the 24-hour electrocardiogram was to differentiate sinus tachycardias from arrhythmias. There were two main reasons for this difficulty. Firstly, at high heart rates P waves were often obscured and the single lead nature of the recording did not help. Secondly changes in electrode contact leading to variation in QRST configuration gave the appearance of aberrant ventricular conduction (Fig. 9); measurement of RR intervals before and after the onset of QRST wave changes may help interpretation.

(C) DEATHS (Table 6)

Twenty-two (18%) of the 120 patients have died and seven of these were late deaths. Two of these late deaths were associated with pulmonary

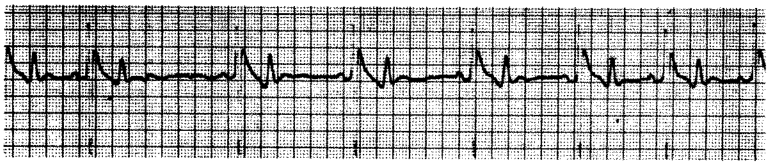

Fig. 7 *24-hour electrocardiogram showing sinus bradycardia of 39/minute (as measured over five beats) and including an RR interval of 1·80 seconds. The biphasic T wave is an artefact of the playback unit of the analyser. Similar rates were found in the 24-hour electrocardiograms of normal children aged 7 to 12 years.*

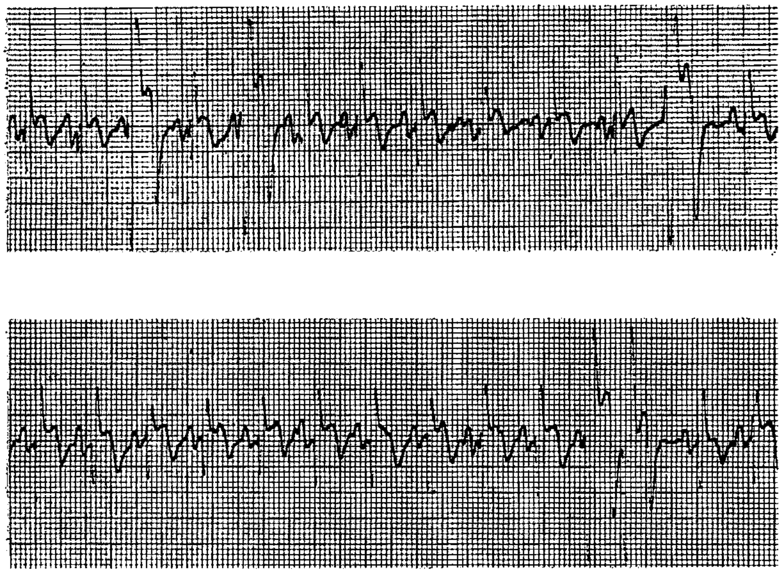

Fig. 8 *24-hour electrocardiogram showing frequent ventricular premature beats with two in succession at the end of the recording. There is no relation between these premature beats and the P waves; there is a constant coupling interval (0·4 seconds), and the QRS configuration is abnormal with ST and T wave changes.*

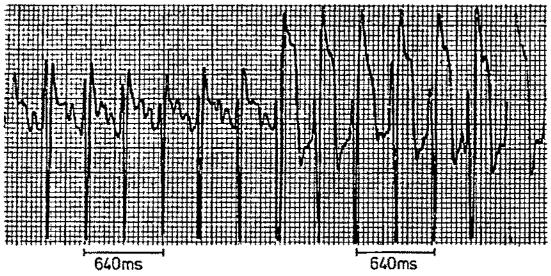

Fig. 9 *24-hour electrocardiogram showing spontaneous variation in ST wave configuration giving the superficial appearance of a tachyarrhythmia. There is no change in rate but the P wave is obscured by an increase in the low frequency T wave. This phenomenon is common and probably results from changes in electrode contact.*

vascular disease, but five patients, with an apparently good surgical result, died suddenly and unexpectedly with no adequate cause found at necropsy. Four of these five had conduction disturbances or arrhythmias documented on standard or 24-hour electrocardiograms while the fifth patient had a normal standard electrocardiogram but had not been studied on a 24-hour tape. The three patients dying after complex Mustard's operation all had conduction abnormalities on standard or 24-hour electrocardiograms in contrast to one of the two patients (without pulmonary vascular disease) dying after simple Mustard's operation. As previously indicated in this patient, a conduction disorder (PR interval 0·24 s) had been present before operation.

Table 5 *Additional postoperative 24-hour electrocardiograph results on nine patients who had complicated Mustard's operation*

Age at operation	*Type of operation*	*Postoperative*		*Time of recording (postoperatively)*	*Outcome*
		Rhythm	*Lowest rate*		
4 months	VSD repair via ventriculotomy	Continuous sinus rhythm	≥50	2 weeks	Sudden late death†
10 months	Revision operation	SAW, J	45–49	3 years	
18 months	Transatrial VSD	SAW, J, APBs (< 12/h)	≥50	2 years	
2 years	Transatrial VSD repair	Continuous sinus rhythm	≥50	2 years	
2 years	VSD repair via ventriculotomy	SAW, J	45–49	3 years	
6 years	Transatrial VSD	SAW, J	35–39	2 years	
1 month	Transatrial VSD repair	APBs 30/h, J* SAW, J, APBs < 12/h	≥50	3–6 months 1 year	Sudden late death†
18 months	LV-PA conduit	VPBs 30/h* couplets (Fig. 8)	≥50	3 weeks	Sudden late death
3 years	Transatrial VSD	SVT 300/min*	45–49	6 months 1 year	

*, abnormal arrhythmias; APB, atrial premature beats; J, intermittent junctional escape rhythm; SAW, electrocardiographic patterns indistinguishable from sinuatrial Wenckebach block; SVT, supraventricular tachycardia; VPB, ventricular premature beats.
†RBBB and LAD also present.

Discussion

The incidence of arrhythmias and other conduction abnormalities after Mustard's operation for transposition of the great arteries has previously been reported to be between 13 and 100 per cent.[2 3 6] In this study we found that 101 of 105 patients who survived the early postoperative period were in sinus rhythm on standard electrocardiography after a modified Mustard's operation designed to avoid the sinus node and atrioventricular conduction tissues.

Furthermore, one of the four patients not in sinus rhythm had complete atrioventricular block before operation and another first degree atrioventricular block, so that of patients discharged from hospital whose preoperative standard electrocardiogram showed sinus rhythm and normal atrioventricular conduction, 98 per cent were in sinus rhythm postoperatively.

A standard 12 lead electrocardiogram, however, records only a small period of time. Twenty-four-hour electrocardiograms, as previously described in other studies,[6 7] are the most effective means of detecting and quantifying arrhythmias after Mustard's operation. We were not surprised, therefore, to find more arrhythmias in our series using this technique. Thus in 43 patients whose standard electrocardiograms showed sinus rhythm after simple Mustard's operation, 24-hour recordings showed additional acquired arrhythmias in four (9%, confidence limits 2 to 22%). However, in 15 who had complex procedures an additional five patients showed acquired arrhythmias on 24-hour recordings (33%, confidence limits 12 to 62%). There seems to be a real difference in the occurrence of arrhythmias on 24-hour recordings in simple and complex Mustard's procedures. However, perhaps because the numbers are small, this is not supported by statistical analysis ($P < 0{\cdot}10$, $\chi^2 = 3{\cdot}237$). Of the 19 patients in the groups who had both pre- and postoperative 24-hour recordings, acquired and abnormal arrhythmias were detected in one of 13 having simple Mustard's operation alone and in two of six undergoing complex procedures.

It is most important when analysing 24-hour electrocardiograms not to ascribe all arrhythmias detected to surgical intervention, as have others.[6 7] We have recently reported the occurrence and patterns of arrhythmias on the 24-hour electrocardiogram in 134 normal healthy neonates,[10] and have additional data[11] on 92 healthy schoolchildren. Table 7 shows that electrocardiographic patterns indistinguishable from sinuatrial Wenckebach block, 2:1, and complete sinuatrial block, junctional escape rhythms, and atrial premature beats of less than 12 per hour are frequently found in the normal population.

Similarly, in Table 7 we have documented episodes of bradycardia described in the normal population which have heart rates previously interpreted by other workers (when found after Mustard's operation) as being acquired and abnormally slow. These findings in healthy infants and children are similar to those of Brodsky *et al.*[14] who showed similar rhythm patterns and rate variations in healthy adults.

The relatively few acquired arrhythmias in our postoperative patients are not only the result of excluding certain rhythm and rate patterns on the grounds that they occur in the normal population, or that they are present before operation. The low prevalence appears to be related to certain aspects of the surgical approach. For instance, the techniques of cannulation of superior and inferior vena cavae and the suturing of the periphery of the baffle to the cut edge of the atriotomy are designed

Table 6 *Seven late deaths after simple and complex Mustard's operation on 120 children*

Type of operation	*Time after operation (months)*	*Cause of death*	*Preop conduction*	*Postop conduction*
Simple	14	Pulmonary vascular disease	Normal	Normal
Simple	4	Pulmonary vascular disease	Normal	Normal
Simple	5	Probably an arrhythmia	1° AV block PR 0·24 s	Complete AV block QRS 0·06 s
Simple	32	Unknown	Normal	Normal*
Complex (ventriculotomy)	3	Probably an arrhythmia	Normal	RBBB + LAD (–90°)
Complex (transatrial VSD repair)	22	Probably an arrhythmia	Normal	RBBB + LAD (–135°)
Complex (LV-PA conduit)	1	Probably an arrhythmia	Normal	Frequent VPBs (30/h)† two in succession

*, no 24-hour electrocardiographic recording; †, on 24-hour electrocardiographic recording; AV, atrioventricular; RBBB, right bundle-branch block; LAD, left axis deviation; VPB, ventricular premature beats.

Table 7 *Summary of 24-hour electrocardiographic findings on healthy neonates aged 1 to 14 days and healthy children aged 7 to 11 years*

	Neonates (n=134)	*Children (n=92)*
Highest heart rate (measured over nine beats)	175 ±19	164 ±16
Lowest heart rate (measured over nine beats)	93 ±12	*56 ±6
Maximum duration of bradycardia < mean lowest rate	Not measured	40 min
Frequency of junctional rhythm	19%	46%
Maximum duration of junctional rhythm	Not measured	25 min
Frequency of PP interval patterns indistinguishable from		
(1) Sinus arrest or complete SA block	5%	8%
(2) 2:1 SA block	11%	37%
(3)*Wenckebach SA block	32%	46%
1° AV block (PR > 0·20 s)	0%	10%
Mobitz type I AV block	0%	3%
Premature beats < 1/h	10%	21%
Premature beats > 1/h	4%	0%

to avoid damage to the sinus and atrioventricular nodes as well as to their blood supply. The advantages of these techniques have previously been stressed by others.[4 14 15] In some reports, the high incidence of atrial arrhythmias after Mustard's operation has been attributed to transection of purported specialised internodal conduction pathways believed to be present in the atrial walls.[16] The operation used in our patients involves a long coronal incision throughout most of the right and part of the left atrial wall transecting the crista terminalis. In addition, most of the atrial septum is removed. Despite this, after operation a large majority of our patients are in sinus rhythm with normal atrioventricular conduction. This is consistent with the view that discrete specialised pathways are not present[17 18] but that conduction from the sinus node to the atrioventricular node occurs through 'working' atrial myocardium.

It is significant that four of the seven late deaths in our series were sudden and associated with arrhythmias or conduction disorders. Pulmonary vascular disease associated with intercurrent illness accounted for two further deaths. Both patients with bifascicular block pattern on the postoperative electrocardiogram died suddenly. This indicated the need for further electrophysiological studies in patients acquiring this conduction abnormality postoperatively. Thus we agree with El Said *et al.*[5] that intracardiac electrophysiological studies are indicated in all patients after Mustard's operation with conduction disorders on the standard electrocardiogram pre- or postoperatively. Permanent pacemaker implantation may be necessary in some.

In our opinion if the true prevalence of dangerous late arrhythmias is to be determined, 24-hour electrocardiograms should be recorded on all postoperative patients.

Our study suggests that by using a modification of Mustard's operation,[19] postoperative conduction disorders and arrhythmias may be largely avoided. In diagnosing these arrhythmias, normal data from healthy children should be taken into account. None the less, despite the low incidence of arrhythmias in our series, some of the sudden late deaths, particularly those associated with complex procedures, appear to result directly from acquired arrhythmias and may well be preventable.

Dr Southall is supported by a grant from the Board of Governors of the Brompton Hospital, National Heart and Chest Hospitals. The 24-hour electrocardiographic equipment was supplied by the British Heart Foundation. We would like to thank Dr Prudence Mitchell for helping with the analysis of the 24-hour recordings.

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Br Heart J 1980; **43:** 31–37

Echocardiographic criteria for Ebstein's anomaly of tricuspid valve

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SUMMARY The diagnostic echocardiographic features of Ebstein's malformation of the tricuspid valve have been evaluated in two groups of patients, using M-mode and two-dimensional techniques. The first group consisted of nine patients in whom previous M-mode studies had suggested the existence of Ebstein's anomaly. The second group consisted of 20 patients, all suffering from right heart overload, in whom Ebstein's malformation was excluded at open heart surgery. The M-mode studies disclosed that none of the criteria currently employed could be considered diagnostic. A delay in tricuspid valve closure of more than 65 ms, considered the most reliable indicator, was also present in eight of 20 'controls'. The characteristic anatomical feature, that is distal displacement of the septal tricuspid leaflet, was never identified with certainty using M-mode echograms, in contrast to two-dimensional echograms which showed a high degree of accuracy. Two-dimensional techniques disclosed an abnormal insertion in six of nine patients in the first group, while a normal insertion was positively identified in 13 of 14 patients with right heart overload. In two of the nine patients in whom Ebstein's anomaly was suggested by M-mode criteria, a normal septal origin was identified and all further attempts to substantiate this diagnosis failed. In one patient from the first group, the two-dimensional study was inconclusive regarding positive identification of the septal origin. Open heart surgery showed a normal origin of the septal leaflet, though the valve was plastered to the septal surface by short chordae. Only once among 14 'controls' was the septal attachment inconclusively identified with the two-dimensional echograms. Surgery, however, excluded the presence of Ebstein's anomaly in this patient. Two-dimensional echocardiography, aiming at visualising the septal origin of the tricuspid valve, thus seems to be useful in establishing a diagnosis of Ebstein's malformation of the tricuspid valve.

The clinical diagnosis of Ebstein's anomaly of the tricuspid valve is notoriously difficult, both with invasive and non-invasive investigations. The problem relates to the fact that Ebstein's anomaly, though an entity in itself, constitutes an anatomical spectrum with regard to the extent and degree of the valvar abnormality.[1–3] The anomaly is characterised by distal displacement of the septal attachment of the valve, a feature which may extend on to the inferior part of the tricuspid valve, and is almost always combined with various degrees of valve dysplasia.

The echocardiographic diagnosis of Ebstein's anomaly, using M-mode techniques, depends on the identification of an increase in motion amplitude of the anterior tricuspid valve leaflet, an increase in the dimensions of the right ventricular cavity, the presence of paradoxical septal motion, the ability to record the tricuspid valve more to the left of the sternum than usual, and a delay in closure of the tricuspid valve as compared with that of the mitral valve.[4–10] However, it is not certain how reliable these indices are as diagnostic criteria. This is an important question since the truly diagnostic criterion, that is the distal displacement of the attachment of the septal leaflet, is not readily obtained with the M-mode echogram. As recently stated, two-dimensional methods may prove to be of value in this respect, since this technique enables the actual identification of the abnormal origin of the valve.[8 11]

It is for this reason that we have employed a two-dimensional echocardiographic technique to restudy a group of nine patients in whom the diagnosis

Received for publication 20 August 1979

of Ebstein's anomaly of the tricuspid valve had previously been suggested from the currently accepted M-mode echographic criteria. In order to assess these criteria another 20 patients, known to have right ventricular volume overload resulting from a variety of causes other than Ebstein's anomaly, were also studied.

Subjects and methods

The material for this study consisted of two groups of patients. The first group was composed of nine patients (six male and three female) ranging in age from 16 to 56 years (average 33 years), all of whom were considered to have Ebstein's anomaly of the tricuspid valve. This presumptive diagnosis had been based on identification of at least two of the following five M-mode criteria[4–10]: an amplitude of the anterior tricuspid valve leaflet motion of 20 mm or more; a right ventricular dimension of 30 mm or more; paradoxical septal motion defined as movement parallel to the motion of the echo from the posterior heart wall during ventricular systole[12]; lateral displacement of the tricuspid valve, defined as the situation in which the tricuspid valve motion can be recorded more to the left of the sternum than usual, taking the left parasternal line as the borderline; and a delay in closure of the tricuspid valve of 65 ms or more, as compared with that of the mitral valve.

In each of these nine patients invasive studies were done in an attempt to verify the presumptive diagnosis.

The second group comprised 20 patients (eight men and 12 women) ranging in age from 21 to 66 years (average 38). They were selected because cardiac catheterisation had shown right heart overload in each. In 13, this was the result of an isolated atrial septal defect of the fossa ovalis type, and in two of an atrial septal defect complicated by partial anomalous pulmonary venous connection; another four had tricuspid regurgitation in the presence of longstanding mitral regurgitation and/or stenosis. One patient had an atrial septal defect in the presence of pulmonary stenosis. In each patient the possibility of Ebstein's anomaly had been ruled out at open heart surgery.

The same echographic studies were performed in both groups. The M-mode studies were performed with the echocardiovisor 01, and recorded on a line scan recorder (Honeywell visicorder 1856) using light-sensitive paper (Kodak type 1895). The tracings were recorded at paper speeds of both 2·5 and 5 cm/s, in order that precise timing in the measurements might be made. The two-dimensional images were made with a dynamically focused multiscan system.[13]

ANATOMY

In order to appreciate the diagnostic possibilities of both M-mode and two-dimensional echocardiograms for Ebstein's anomaly, it is necessary to recall the basic anatomical derangements in this condition.

The disease is characterised by two main features.[1–3] First, part of the basal attachment of the tricuspid valve is displaced distally, thereby creating a so-called atrialised part of the right ventricle (Fig. 1). Distal displacement affects the septal leaflet but this varies in extent with the inferior leaflet. The anterior leaflet, on the other hand, always originates from the annulus fibrosus. The second anatomical feature of Ebstein's anomaly is dysplasia of the valve, often characterised by a sail-like deformity of the 'non-displaced' anterior leaflet. However, as with distal displacement, the extent and degree of valve dysplasia may vary considerably from one patient to the other.[2 3] In some instances the 'sail-like' anterior leaflet may be free floating, while in others the leaflet is 'plastered' to the right ventricular free wall. In the latter circumstances the valve leaflet can be much restricted in its mobility. In rare circumstances, moreover, the septal inferior and anterior leaflets may become continuous, thus creating a severe inlet obstruction to the right ventricular outlet; a situation that clinically may mimic 'classical' tricuspid atresia.

From the point of view of echographic identification of Ebstein's anomaly, distal displacement of the septal origin of the valve seems by far the best criterion since dysplasia in itself is not readily distinctive (Fig. 1).

Results

The echographic data obtained from the nine patients initially diagnosed as having an Ebstein's anomaly of the tricuspid valve are shown in the Table. The M-mode studies revealed that the motion amplitude of the anterior tricuspid valve leaflet was increased in all, whereas in eight there was an abnormal increase of the right ventricular dimension. Lateral 'displacement' of the tricuspid valve was obvious in seven patients, while this feature was inconclusive in two. Delay in closure of the tricuspid valve of more than 65 milliseconds was present in eight and paradoxical septal motion in six patients.

Deliberate attempts to identify the septal attachment of the tricuspid valve using the M-mode method were unsuccessful in all nine patients. In only one (case 7) was the suggestion of a low insertion raised, since the septal tricuspid valve leaflet was recorded only when the ultrasound beam

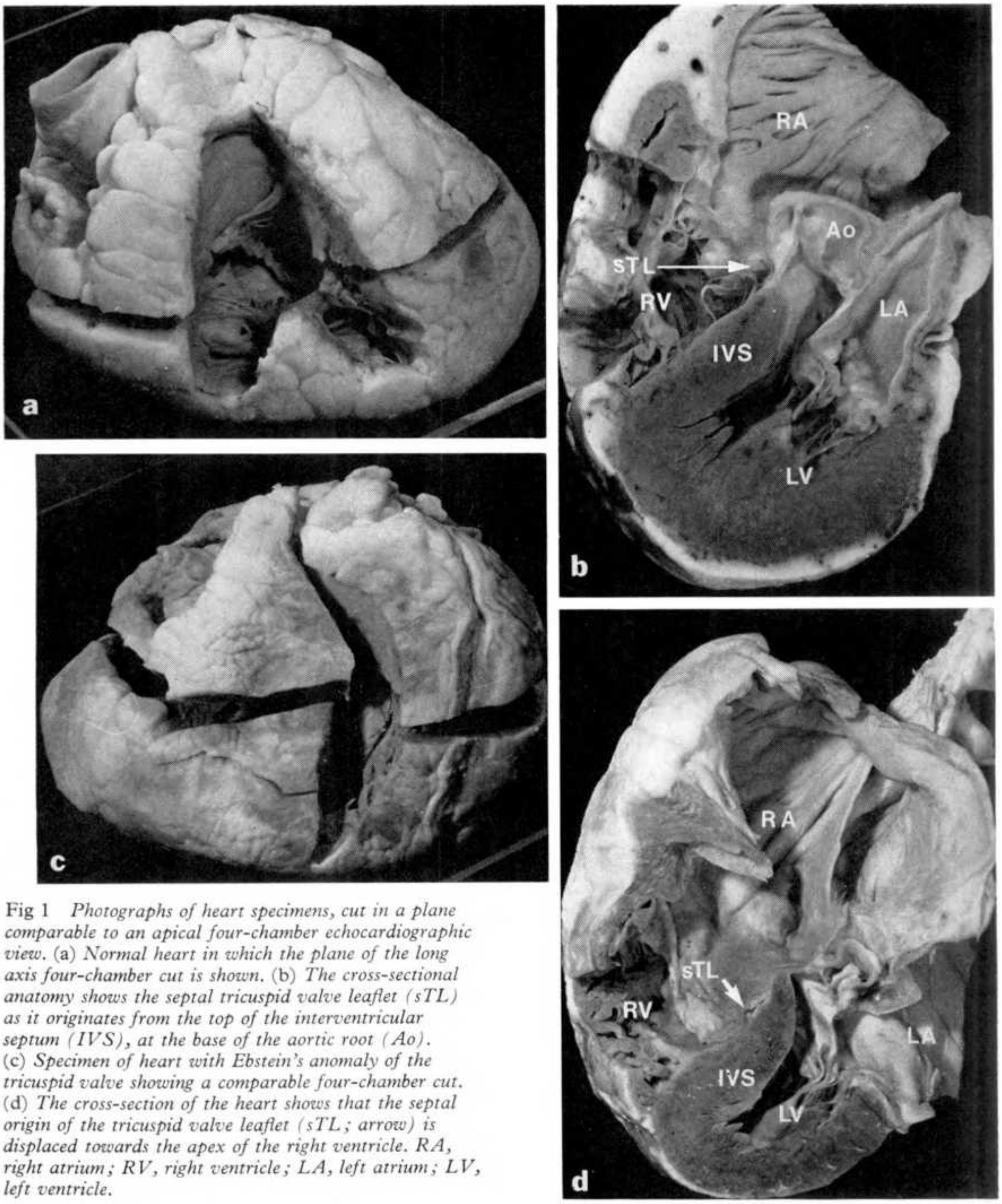

Fig 1 *Photographs of heart specimens, cut in a plane comparable to an apical four-chamber echocardiographic view.* (a) *Normal heart in which the plane of the long axis four-chamber cut is shown.* (b) *The cross-sectional anatomy shows the septal tricuspid valve leaflet (sTL) as it originates from the top of the interventricular septum (IVS), at the base of the aortic root (Ao).* (c) *Specimen of heart with Ebstein's anomaly of the tricuspid valve showing a comparable four-chamber cut.* (d) *The cross-section of the heart shows that the septal origin of the tricuspid valve leaflet (sTL; arrow) is displaced towards the apex of the right ventricle. RA, right atrium; RV, right ventricle; LA, left atrium; LV, left ventricle.*

swept close to the right ventricular apex (Fig. 2). In some instances an accumulation of echoes was observed at the right ventricular site of the interventricular septum, but these echoes were never positively identified as representing a displaced valve leaflet (Fig. 3a).

Two-dimensional echograms, on the other hand, visualised the septal attachment of the tricuspid

Table *M-mode and two-dimensional data obtained in nine patients suspected of having Ebstein's anomaly of tricuspid valve according to current M-mode criteria* (see text)

	M-mode data						*Two-dimensional data*		
Case no.	*Right ventricular dimension (mm)*	*Amplitude aTL (mm)*	*Paradoxical septal motion*	*Lateral displacement TV*	*Delayed closure TV*	*Distal displacement of the sTL*	*Increased amplitude aTL*	*Sail-like motion aTL*	*Distal displacement sTL*
1	70	50	+	+	76	NV	+	+	+
2	55	48	+	+	80	NV	+	+	+
3	22	43	+	?	120	NV	–	–	NV
4	40	42	–	?	40	NV	+	–	–
5	36	35	–	+	100	NV	+	+	+
6	88	45	+	+	122	NV	+	+	+
7	50	33	+	+	160	?	+	–	+
8	46	33	–	+	180	NV	+	+	+
9	45	42	+	+	80	NV	+	+	–

Abbreviations: aTL, anterior tricuspid valve leaflet; TV, tricuspid valve; sTL, septal tricuspid valve leaflet; +, present; – , absent; ?, questionable; NV, not visualised.

valve in eight patients and distal displacement was positively identified in six. The 'ideal' position of the transducer, enabling positive identification, varied from one individual to the other and encompassed classical long axis, cross-sectional, and apical views (Fig. 3b and c, and 4a). In two patients (Table; cases 4 and 9) the septal attachment was identified at a normal level, that is close to the aortic root (compare Fig. 4a and b), at the junctional level between mitral valve, interventricular septum, and interatrial septum; catheter studies confirmed the presence of tricuspid regurgitation, but in neither was there any indication of Ebstein's anomaly. Simultaneous pressure and electrical recordings did not disclose the presence of an atrialised part of the right ventricle. In one patient (Table; case 3) the two-dimensional echogram did not visualise the septal attachment of the tricuspid valve. This patient is of particular significance, since cardiac catheterisation studies disclosed a large atrial septal defect with tricuspid regurgitation, while Ebstein's anomaly could not be excluded with certainty from the angiograms. At open heart surgery it was noticed that the septal tricuspid valve leaflet took a normal origin from the right-sided annulus fibrosus, but the leaflet was for its greater part plastered to the right ventricular septal wall by short chordae. These observations suggest that this anomaly may fit within the category of Ebstein's anomaly of the tricuspid valve. Cardiac catheterisa-

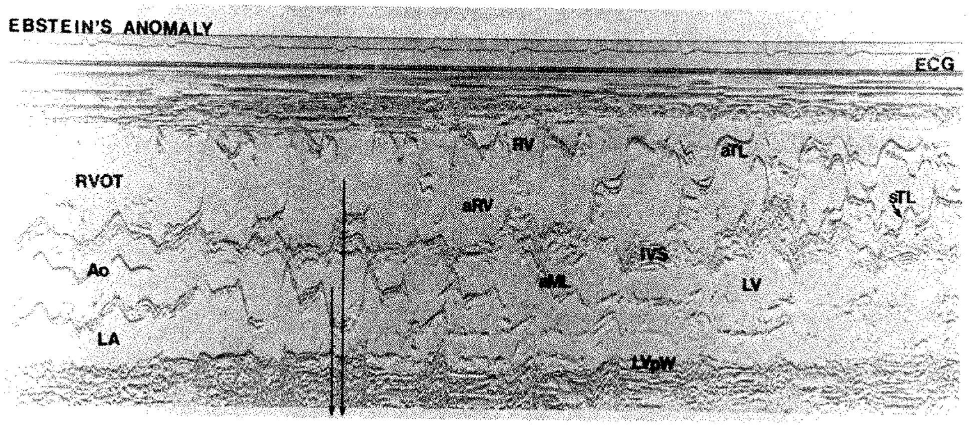

Fig. 2 *A male patient, 23 years of age (Table; case 7) with proven Ebstein's anomaly. In the M-mode recording the septal tricuspid valve leaflet (sTL; arrow) appeared only when the ultrasound beam swept close to the right ventricular apex. The long and short arrows indicate the time of closure of the tricuspid and mitral valves, respectively. Note the delayed closure of the former. RVOT, right ventricular outflow tract; Ao, aorta; LA, left atrium; aML, anterior mitral valve leaflet; LV, left ventricle; IVS, interventricular septum; RV, right ventricle; aRV, atrialised right ventricle; aTL, anterior tricuspid leaflet; sTL, septal tricuspid leaflet; LVpW, left ventricular posterior wall.*

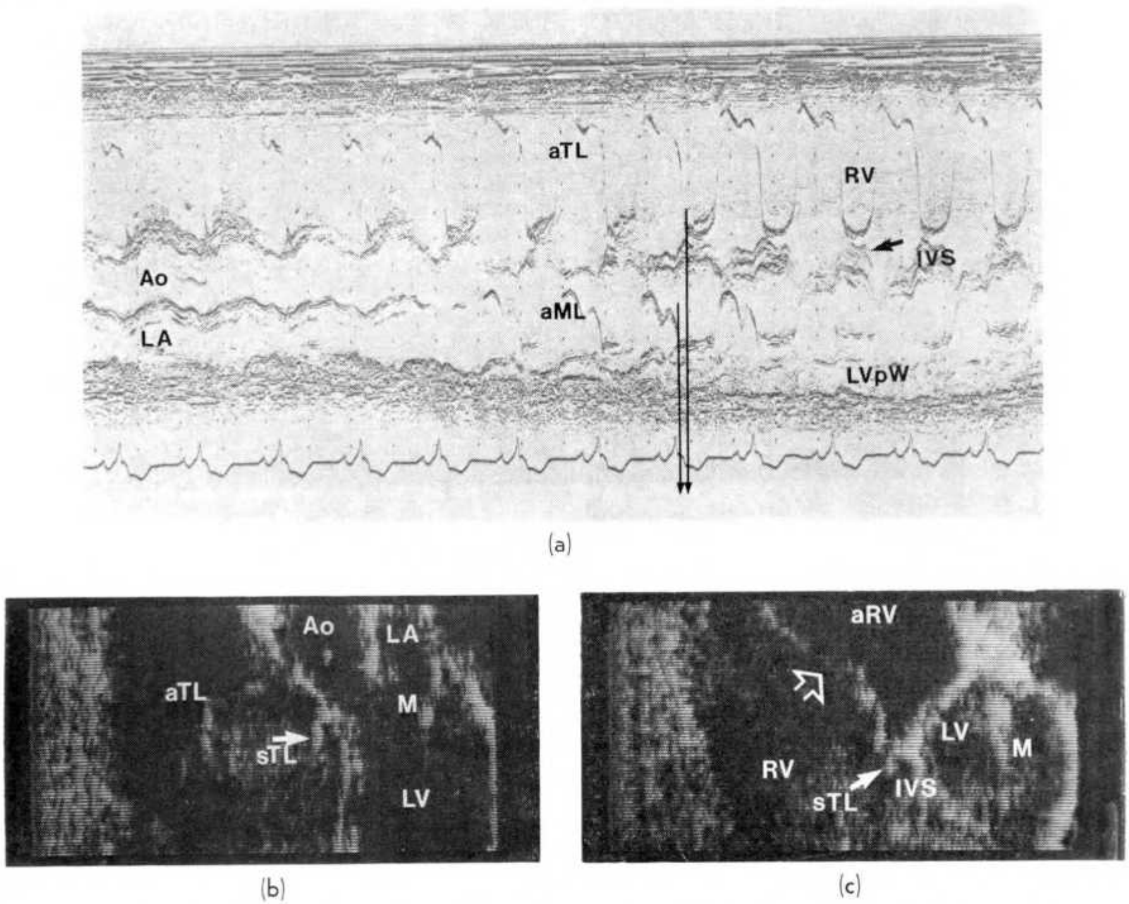

Fig. 3 *A female patient, 22 years of age (Table; case 2) with proven Ebstein's anomaly of the tricuspid valve.* (a) *M-mode tracing which discloses an increase in the right ventricular dimension and the motion amplitude of the anterior tricuspid leaflet, delayed closure of the tricuspid valve of 80 ms, and paradoxical movement of the interventricular septum. The arrow points to multiple echoes at the right ventricular site of the interventricular septum. Abbreviations as in* Fig. 2. (b) *and* (c) *Two-dimensional long axis and cross-sectional views, respectively, of the same patient. The septal tricuspid leaflet (sTL; arrow) takes an abnormal 'low' insertion from the interventricular septum (IVS). The atrialised part of the right ventricle (aRV) is well seen in* (c). *Note the large anterior tricuspid leaflet in both views (aTL in* 3b *and open arrow in* 3c*). Ao, aorta; LA, left atrium; LV, left ventricle; M, mitral valve.*

tion in the remaining six patients, that is those with positive two-dimensional echographic identification of Ebstein's disease, were all in accord with this diagnosis.

In the second group of patients, that is those with right ventricular overload, the M-mode studies also showed a high percentage of positivity for the 'Ebstein's' criteria (vide supra). The right ventricular dimensions were increased in all and in eight the amplitude of the anterior tricuspid valve leaflet motion was also increased. Paradoxical septal motion was present in 16, and lateral displacement of the tricuspid valve was identified in eight. Delayed closure of the tricuspid valve, as defined previously, was present in eight patients and ranged from 70 to 260 milliseconds. Distal displacement was not recognised in any of these 20 patients.

Two-dimensional echocardiograms were obtained from 14 of these 20 patients. In 13, a normal septal origin was recorded (Fig. 4b). On only one occasion was the septal origin not visualised and that was in a patient suffering from an atrial septal defect of the fossa ovalis type with mild pulmonary stenosis.

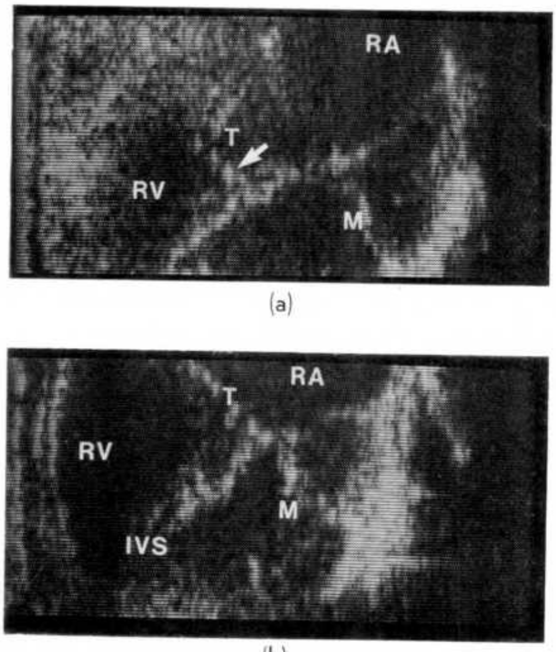

Fig. 4 *Two-dimensional echocardiograms showing similar apical views in a patient with Ebstein's anomaly (*Fig. 4a*) and a patient with right heart overload resulting from an atrial septal defect (*Fig. 4b*). In this particular plane of sectioning the mitral (M) and tricuspid (T) valves normally should meet at the site of junction between the interventricular septum (IVS) and the interatrial septum (*Fig. 4b*). Note the distal origin (arrow) of the septal tricuspid valve in Ebstein's anomaly* (Fig. 4a).
RA, right atrium; RV, right ventricle.

Discussion

The present studies unequivocally show that the current M-mode criteria for the diagnosis of Ebstein's anomaly of the tricuspid valve are in themselves non-diagnostic, most of the indices appearing related to secondary haemodynamic effects rather than an anomaly of the valve. Conditions characterised by volume overload of the right ventricle may lead to an increase in right ventricular dimension and paradoxical septal movements. Moreover, the anterior leaflet of the tricuspid valve under these circumstances is easily picked up by the transducer, a feature which may be recorded as an increased amplitude of leaflet motion. In itself the amplitude recorded is highly dependent on the position of the transducer. In fact, this is one of the major reasons why a precise delineation of the range of normality has not yet been established. We accept, therefore, that our criterion of 20 mm is arbitrary, but in our experience this value constitutes an average of 'normality' for adult patients. Most authors agree that delay in closure of the tricuspid valve of more than 65 milliseconds, as compared with that of the mitral valve, is a reliable diagnostic indication of Ebstein's anomaly.[4–10] It is significant, therefore, that eight of our patients from a series of 20 (40%) without Ebstein's anomaly but with right heart volume overload had such a delay in tricuspid valve closure. We conclude that even a delay of over 65 milliseconds in tricuspid valve closure cannot be diagnostic of Ebstein's anomaly. We agree, however, that a combination of these M-mode data should alert one to the possibility of Ebstein's anomaly, making subsequent investigations mandatory. We believe that two-dimensional echocardiograms play a paramount role, based on the understanding of the main anatomical feature of echocardiographic significance, that is the distal displacement of the septal origin of the tricuspid valve. Recently, Matsumoto *et al.*[8] and Ports *et al.*,[11] using a two-dimensional method, have diagnosed Ebstein's anomaly from this particular feature. Our results further indicate that positive identification of an abnormally low insertion of the septal tricuspid valve leaflet is indeed a reliable indicator of Ebstein's anomaly. Among our nine patients in whom the combination of M-mode data had suggested Ebstein's anomaly, there were six in whom the two-dimensional method actually showed distal displacement. In two patients, however, a normal septal origin of the valve was recorded and it is of interest that extensive intracardiac catheter studies failed to substantiate further this diagnosis. In one patient the septal attachment was not visualised with the two-dimensional technique. This inconclusive finding is significant since open heart surgery in this patient disclosed an abnormal septal valve leaflet. The valve took its normal origin, but the leaflet was for its greater part plastered to the septal surface. One could argue that this is not Ebstein's anomaly of the tricuspid valve, but, on the other hand, this observation also serves to indicate that even with two-dimensional techniques some extreme variants of Ebstein's anomaly will not be recognised. For instance, this might occur where extreme distal displacement of the septal and inferior leaflets is associated with a membrane-like continuum into the anterior leaflet, thereby creating a so-called imperforate Ebstein anomaly. Nevertheless, the two-dimensional method seems accurate as further substantiated by the findings in our group of patients without Ebstein's anomaly. While the M-mode data in some of them suggested the possibility of Ebstein's anomaly, the two-dimensional echograms showed a normal septal origin in almost all. In only one patient was the septal origin not visualised —a patient suffering from an atrial septal defect and mild pulmonary stenosis.

To obtain the best results, the transducer should be placed in a transverse position close to the apex of the heart and perpendicular to the plane of the long axis view. The operator should direct the plane of the image slightly upwards, so that the aortic root region is clearly visualised. The plane of 'sectioning' thus fluctuates between the standard cross-sectional and apical four-chamber views. Abnormalities in the septal attachment of the tricuspid leaflet may thus be identified and one might expect even a small rim of dysplastic and displaced valve tissue to be detected. We, therefore, believe that the two-dimensional echocardiogram is valuable in patients suspected of having Ebstein's anomaly of the tricuspid valve.

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Br Heart J 1980; **43:** 38–44

Value of M-mode echocardiography for non-invasive diagnosis of Ebstein's anomaly

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SUMMARY M-mode echocardiographic studies were performed in 11 patients, most of them adults, with Ebstein's anomaly of the tricuspid valve, proven by cardiac catheterisation. Simultaneous recordings of the tricuspid and mitral valves were obtained in all cases, the transducer position being outside the left midclavicular line in seven patients. Tricuspid valve closure followed mitral valve closure in all cases, with an interval ranging between 0·04 and 0·14 s. Since, in more than 8500 routine echocardiographic studies a valve closure interval between 0·09 and 0·12 s was seen in only one patient without Ebstein's anomaly, an interval of 0·065 s or more should be regarded as diagnostic of Ebstein's disease; however, an interval shorter than 0·065 s does not exclude this diagnosis.

In all patients a paradoxical septal movement was found. Two patients showed an atypical three-peaked diastolic pattern of movement of the anterior tricuspid leaflet and one patient also showed mitral valve prolapse.

Pathological tricuspid valve closure delay, shown by echocardiography, makes it possible to diagnose Ebstein's anomaly in many cases without resort to cardiac catheterisation which has a relatively high risk in this disease.

The tricuspid valve anomaly first described by Ebstein in 1866[1] is found in less than 1 per cent of patients with congenital malformations of the heart.[2] The principal anatomical lesion consists of a downward displacement of varying degree of the septal and posterior leaflets of the tricuspid valve. The clinical course, radiological, electrocardiographic, and phonocardiographic findings, and prognosis are well known.[3–5] Cardiac catheterisation and angiocardiography usually confirm the suspected clinical diagnosis; however, in this condition, these procedures are associated with an increased risk, with mortality of approximately 3·5 per cent.[5] Echocardiography, a non-invasive diagnostic method with a high degree of accuracy, is thus of special importance in this disease.

Since Lundström's first description in 1969, M-mode echocardiographic findings in Ebstein's anomaly have been described[6–14]; however, most of these authors reported only a few cases and only a few tried to analyse the echocardiographic features systematically. As the results of these studies were inconsistent, particularly in respect of the pattern of movement of the tricuspid valve, the echocardiographic signs of this anomaly were carefully analysed in seven adults and four children; all of whom had had cardiac catheterisation in our laboratory during recent years.

Received for publication 27 March 1979

Subjects and methods

PATIENTS

Eleven patients were studied (seven female and four male; aged between 1 and 41 years, average 21 years). The diagnosis of Ebstein's anomaly was confirmed in all by right heart catheterisation (including right ventriculography in eight cases) and in two cases also by necropsy; in seven patients left heart catheterisation was also performed. Five patients had a secundum atrial septal defect, and three a patent foramen ovale (Table 1). At the time of examination, all patients were in sinus rhythm, five with incomplete and six with complete right bundle-branch block.

METHODS

M-mode echocardiograms were recorded in the

Table 1 *Echocardiographic measurements in patients with Ebstein's anomaly*

Case no.	Age/sex (y)		*ATL*			*AML*			McTc (s)	MdTd (s)	MoTo (s)	HR (b/min)	Associated cardiac lesions	ECG
			A (mm)	EF slope (mm/s)	OV	A (mm)	EF slope (mm/s)	OV						
1	1	F	27	76	264	13	94	148	0·09	–0·02	0·04	121	ASD II	IRBBB
2	7	M	23	76	303	16	79	156	0·06	0·01	—	113	PFO	IRBBB
3	10	F	36	64	267	23	40	197	0·04	0	0·07	63	ASD II	RBBB, 1° AV block
4	15	F	36	79	287	20	83	323	0·12	0·03	0·03	81	ASD II	RBBB, 1° AV block
5	17	M	27	156	245	27	170	250	0·06	0	0	96	—	IRBBB
6	17	F	48	85	332	28	128	277	0·09	–0·03	0	71	—	IRBBB
7	21	F	29	128	245	18	85	176	0·04	0·05	0·02	95	PFO	RBBB, 1° AV block
8	31	F	30	118	304	31	87	238	0·11	–0·06	–0·05	60	—	RBBB
9	31	F	36	50	224	19	44	109	0·12	0	0·08	77	ASD II, MVP	IRBBB
10	37	M	38	—	278	21	39	122	0·13	0	—	64	PFO	RBBB, 1° AV block
11	41	M	44	61	168	26	49	198	0·14	0·04	0·03	63	ASD II	RBBB
Mean			34·0*	89·3	266·8†	22·0*	81·6	199·5†	0·09	0·006	0·024	82·2		
SD ±			7·6	33·7	41·0	5·5	40·2	66·8	0·04	0·032	0·039	21·3		

* P < 0·001; † P < 0·01.
ATL and AML, anterior tricuspid and mitral leaflets; A, amplitude; EF slope, early diastolic closing slope; OV, opening velocity; McTc, interval between mitral (Mc) and tricuspid (Tc) valve closure; MdTd, interval between mitral (Md) and tricuspid (Td) valve opening; MoTo, interval between maximal opening of mitral (Mo) and tricuspid (To) valve; HR, heart rate;
PFO, patent foramen ovale; MVP, mitral valve prolapse; ASD II, atrial septal defect (secundum type); RBBB, right bundle-branch block; IRBBB, (incomplete) right bundle-branch block; 1° AV block, first degree AV block.

supine position with a 2·25 or 4·5 MHz focused or unfocused transducer using an Echocardiovisor 01 (Organon Teknika, OSS/Netherlands), a Smith-Kline Ekoline 20, or an Irex ultrasonoscope. Recordings were made at paper speeds of 50 and 100 mm/s on high-sensitivity photographic paper. In all patients simultaneous recordings of the anterior tricuspid leaflet and the anterior mitral leaflet were obtained. For this purpose in seven cases an unusual left lateral transducer position was necessary up to the anterior axillary line.

In order to compare our results with those of other investigators,[8] [12] the following points were defined (Fig. 1): point 'd' indicating the beginning of the rapid diastolic opening movement or the end of the slow systolic anterior motion of the anterior leaflets of tricuspid (T) and mitral (M) valves (Td and Md); point 'o' corresponding to the most anterior position of the anterior leaflets at the time of complete opening of each valve (To and Mo); point 'c' representing the most posterior position at the end of diastole or the beginning of systole with closure of the leaflets (Tc and Mc).

From these points, the closing interval (McTc), the opening interval (MdTd), and the interval at maximal opening (MoTo) were measured. In addition, the opening amplitude 'A' (maximal distance c–o), the opening velocity (d–o), and the early diastolic closing slope (EF slope, beginning at point 'o') were measured. End-diastolic diameters (EDD) of the right and the left ventricle were measured at the peak of the R wave of the simultaneously recorded electrocardiogram. Measurements were averaged over three to five cardiac cycles. Interventricular septal motion was analysed with regard to abnormal motion type A (systolic

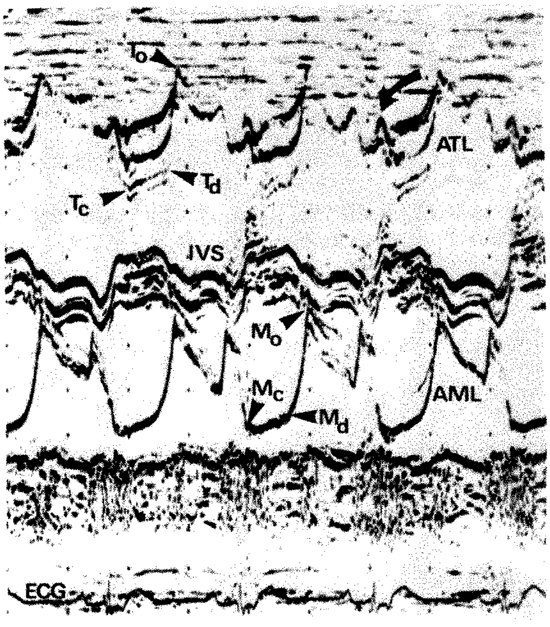

Fig. 1 *Echocardiogram in Ebstein's anomaly. ATL and AML, anterior tricuspid and mitral leaflets; IVS, interventricular septum; Tc and Mc, tricuspid and mitral valve closure; Td and Md, tricuspid and mitral valve opening; To and Mo, point of maximal opening of tricuspid and mitral valve; arrow, additional diastolic opening movement of ATL (see text). ECG, electrocardiogram.*

anterior movement) and type B (reduced posterior movement). Statistical analysis was performed using standard linear regression and Student's t test.

Results

The results are summarised in Tables 1 and 2. In all 11 patients tricuspid valve closure followed mitral valve closure (Fig. 1, 2, 4), the interval McTc varying between 0·04 and 0·14 s (average 0·09 ± 0·04 s). Simultaneous phonocardiographic recordings showed that the moment of tricuspid and mitral valve closure (Tc, Mc) coincided with the tricuspid and mitral components of the first heart sound (Fig. 2 and 3). No significant linear correlation was found between McTc and the amplitude (r = 0·50) or opening velocity of the anterior tricuspid leaflet (r = −0·19), RVEDD (r = 0·33), or ratio RVEDD/LVEDD (r = 0·23).

Tricuspid opening (Td) was found to occur before mitral opening (Md) in three, after in four, and at the same time in four patients. The maximum opening point of the tricuspid valve (To) could not be determined exactly in two cases; in the other nine cases To was found to occur before the maximum opening point of the mitral valve (Mo) in one, after in six, and at the same time in two cases. The maximum amplitude 'A' of the anterior tricuspid leaflet was larger than the maximum amplitude of the anterior mitral leaflet in nine patients (averages for all 11 patients: 34·0 ± 7·6 mm and 22·0 ± 5·5 mm, respectively; P < 0·001). There was a significant negative correlation between heart rate and the amplitude of both the anterior tricuspid leaflet (r = −0·71; P < 0·05) and the anterior mitral leaflet (r = −0·72; P < 0·05).

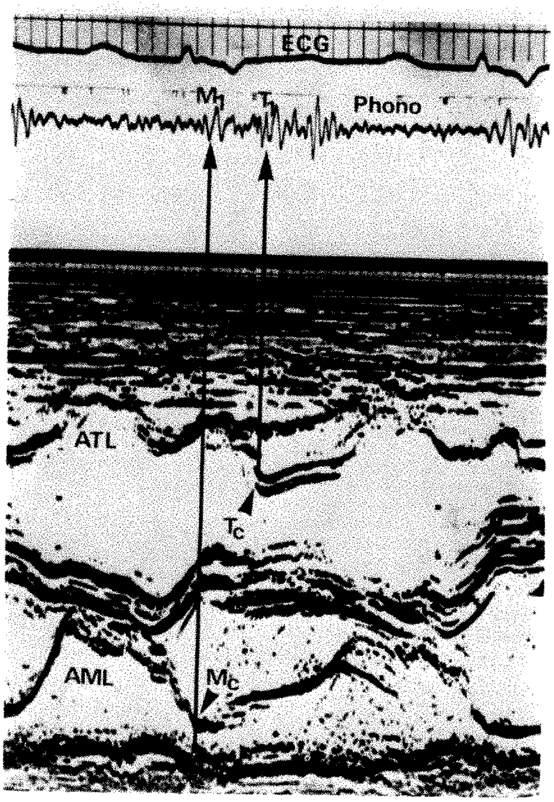

Fig. 2 *Echocardiogram in Ebstein's anomaly. McTc interval, 0·140 s. Mc corresponds with mitral (M1), Tc with tricuspid (T1) component of the first heart sound. Phono, external phonocardiogram.*

Table 2 *Echocardiographic measurements in patients with Ebstein's anomaly*

Case no.	*AT*/*AM*	*SLT*/*SLM*	*OVT*/*OVM*	*IVS*	*RVEDD* (*mm*)	*LVEDD* (*mm*)	*RVEDD*/*LVEDD*
1	2·1	0·8	1·8	A	28	21	1·3
2	1·4	1·0	1·9	A	33	26	1·3
3	1·6	1·6	1·4	A	59	31	1·9
4	1·8	1·0	0·9	A	42	31	1·4
5	1·0	0·9	1·0	A	45	40	1·1
6	1·7	0·7	1·2	A	51	45	1·1
7	1·6	1·5	1·4	A	40	39	1·0
8	1·0	1·4	1·3	A	56	31	1·8
9	1·9	1·1	2·1	A	56	33	1·7
10	1·8	—	2·3	A	58	41	1·4
11	1·7	1·2	0·9	A	53	38	1·4
Mean	1·6	1·1	1·5		47·4*	34·2*	1·4
SD ±	0·3	0·3	0·5		10·5	7·1	0·3

* P < 0·001.

AT and AM, amplitude of ATL and AML; SLT and SLM, early diastolic closing slope of ATL and AML; OVT and OVM, opening velocity of ATL and AML; IVS A, paradoxical septal movement type A; RVEDD and LVEDD, end-diastolic diameter of right and left ventricle.

The early diastolic closing slope of the anterior tricuspid leaflet could not be measured in one case; in three cases this slope was in the lower range of normal or slightly reduced (50 to 64 mm/s). The early diastolic closing slope of the anterior mitral leaflet was similarly slightly reduced in these three cases (40 to 49 mm/s). In five patients the closing slope of the anterior tricuspid leaflet was faster than the slope of the corresponding anterior mitral leaflet, ranging between 118 and 156 mm/s in three cases; in the remaining five patients the closing slope of the anterior mitral leaflet was faster. In the group as a whole there was no significant difference between the closing slopes (tricuspid 89·3 ± 33·7 mm/s, mitral 81·6 ± 40·2 mm/s). The linear correlation between the tricuspid and mitral closing slopes was significant (r = 0·77; P < 0·01), but there was no significant correlation between the closing slopes and heart rates.

Finally, the opening velocity of the anterior tricuspid leaflet (TdTo) was found to be faster than the opening velocity of the anterior mitral leaflet (MdMo) in all but three cases; for the whole group this difference was significant (tricuspid 266·8 ± 41·0 mm/s, mitral 199·5 ± 66·8 mm/s; $P < 0·01$).

Two patients showed an atypical three-peak movement of the anterior tricuspid leaflet: after the late diastolic opening caused by atrial contraction there was an additional opening motion before closure (Fig. 1 and 4).

In all 11 patients RVEDD was larger than LVEDD (47·4 ± 10·5 mm vs. 34·2 ± 7·1 mm; $P < 0·001$), the ratio RVEDD/LVEDD ranging from 1·0 to 1·9. In all patients paradoxical septal movement type A was present.

As an incidental finding one patient showed a conspicuous prolapse of the posterior mitral leaflet on the left ventriculogram, though this was not convincingly shown on the echocardiogram.

Discussion

As a rule in this group of patients it was much easier to locate the anterior tricuspid leaflet than the anterior mitral leaflet, as is usually the case in diseases with right ventricular volume overload. Moreover, in the majority of cases, the transducer position for optimal display of both valves was found to be outside the left midclavicular line. This is in accord with the findings of Farooki *et al.*,[12] who studied more than 2000 neonates and infants with normal hearts and different congenital malformations; these authors considered the ability to record the anterior tricuspid leaflet from outside the left midclavicular line, with the transducer directed inferiorly and leftward, to be specific for Ebstein's anomaly.

Abnormally late tricuspid valve closure has been thought to be diagnostic of Ebstein's anomaly.[6–12 14 15] Farooki *et al.*[12] found the normal McTc in healthy persons to range from 0 to 0·03 s, and Milner *et al.*[14] report normal values from –0·005 to 0·05 s. In both studies, the controls, consisting mostly of patients with congenital malformations with right ventricular volume overload, had McTc not exceeding the normal range (except one case with secundum atrial septal defect and an McTc of 0·06 s reported by Milner *et al.*[14]). These authors regard a tricuspid valve closure delay of more than 0·03 s and 0·065 s, respectively, as specific for Ebstein's anomaly. Lundström[8] in his series of 19 patients considered the upper limit of normal McTc to be 0·03 s; in all his Ebstein patients tricuspid valve closure was late, with McTc at least 0·06 s, the longest interval being 0·17 s. In smaller groups of patients with Ebstein's anomaly McTc was 0·04 s or more.[6 7 9 10]

In our group of 11 patients the McTc ranged from 0·04 to 0·14 s (average 0·09 ± 0·04 s) with a value of 0·06 s or more in nine cases. Thus, our investigation supports previous evidence that in Ebstein's disease the McTc is usually abnormally prolonged, though (depending on the definition of the upper limit of the normal range) some cases may have normal values of this interval. On the other hand, in more than 8500 echocardiographic

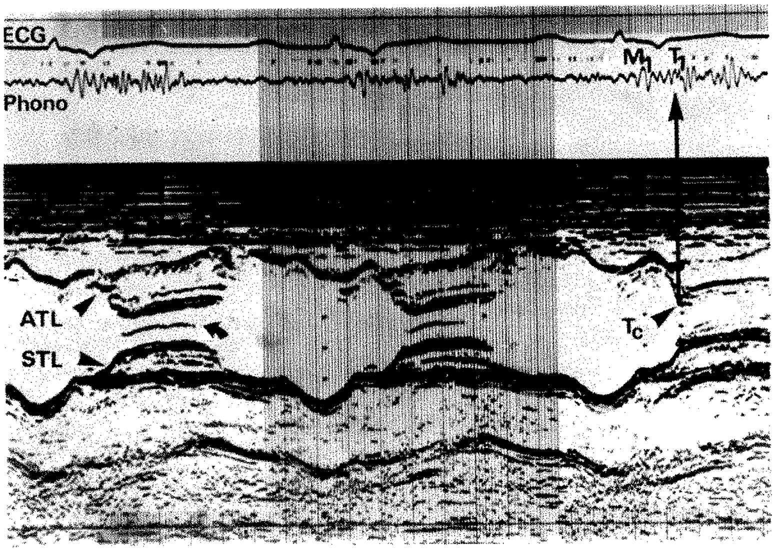

Fig. 3 *Echocardiogram in Ebstein's anomaly with tricuspid regurgitation. ATL and STL, anterior and septal tricuspid leaflets. Incomplete systolic closure of the valve with presumably parts of the third leaflet* (arrow); *M1 and T1, mitral and tricuspid component of the first heart sound.*

studies in our laboratory we have seen only one patient who did not have Ebstein's anomaly but who had McTc between 90 and 120 ms on several occasions (Fig. 5). This patient was a 2-day-old baby who was shown at necropsy to have pulmonary atresia associated with an intact interventricular septum, patent foramen ovale (diameter 2·2 cm), persistent ductus arteriosus, enlarged right and small left ventricle, and tricuspid regurgitation. To our knowledge, this is the first time that such a late closure of the tricuspid valve has been described in the absence of Ebstein's anomaly.[16]

The abnormal delay of tricuspid valve closure in patients with Ebstein's anomaly cannot be explained by the presence and degree of right bundle-branch block alone. Late tricuspid closure was observed by Tajik *et al.*[9] in one patient with Ebstein's anomaly and WPW syndrome type B, but no abnormal delay was found by Milner *et al.*[14] in 25 patients with complete right bundle-branch block alone or by Farooki *et al.*[12] in 14 patients with atrial septal defect and complete right bundle-branch block. On the other hand, Crews *et al.*[7] observed a correlation between width of QRS complex and delay in tricuspid closure in three patients with Ebstein's anomaly and right bundle-branch block. The late closure of the tricuspid valve may be explained by mechanical factors related to the displacement of the enlarged and abnormal tricuspid valve or by an abnormal contraction pattern of the right ventricle.[9, 17]

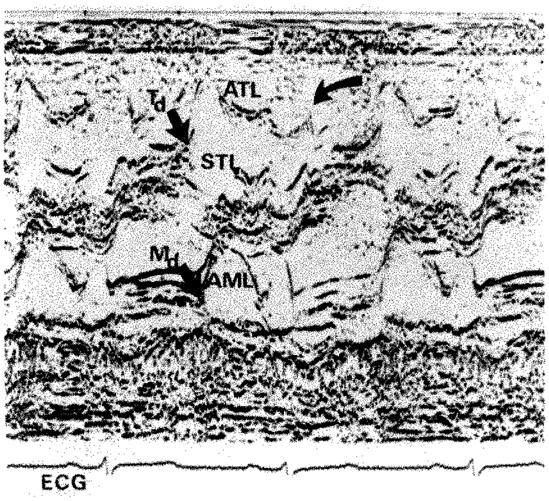

Fig. 4 *Echocardiogram in Ebstein's anomaly. ATL and STL, anterior and septal tricuspid leaflets; AML, anterior mitral leaflet; Td and Md, tricuspid and mitral valve opening points; curved arrow, additional diastolic opening movement of ATL (see text).*

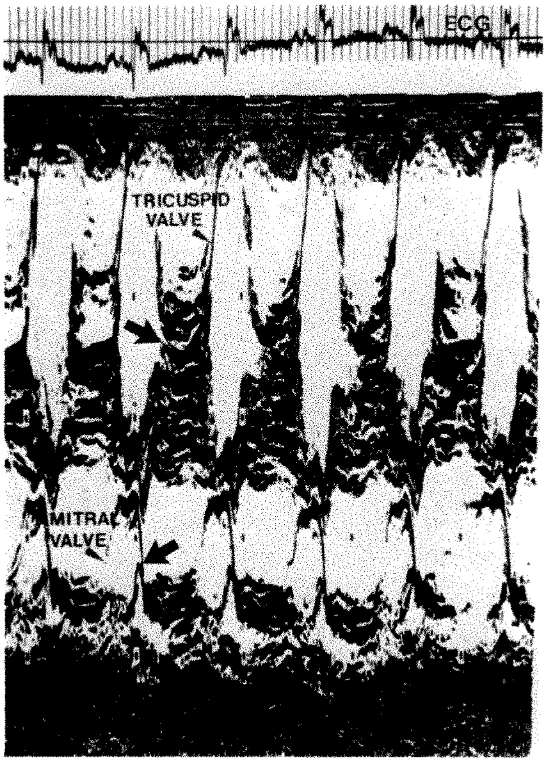

Fig. 5 *Echocardiogram of patient with pulmonary atresia without Ebstein's anomaly (proven by necropsy). Tricuspid valve closure follows closure of mitral valve after 0·09 s (closure points marked by arrows) (see text).*

Two patients showed an atypical diastolic three-peak movement of the anterior tricuspid leaflet. The abnormal McTc in these was obviously the result of the third peak (Fig. 4) which represents an additional opening of the tricuspid valve in late diastole. This abnormal pattern may be a consequence of the premature opening of the pulmonary valve described in cases of Ebstein's anomaly with tricuspid regurgitation.[18] It is possible that the premature pulmonary opening and the resulting right ventricular pressure changes cause a divided opening movement of the tricuspid leaflets during atrial contraction. However, further analysis of simultaneous recordings of the echocardiogram and of pressures in the right atrium and pulmonary artery would be necessary to confirm this explanation.

No significant relation has been found hitherto between McTc and age, associated cardiac lesions, right atrial or right ventricular pressure or dimension, opening velocity, closing slope, or amplitude of the anterior tricuspid leaflet.[12] Our observations confirm these findings in respect of amplitude, opening velocity, closing slope, and RVEDD.

Amplitude, opening velocity, and closing slope of the anterior tricuspid leaflet and the relation of these measurements to the corresponding values of the anterior mitral leaflet do not distinguish patients with Ebstein's anomaly from normals and those with other congenital malformations of the heart.[12] In our patients also these measurements show a wide scatter and overlap with the control values.

Lundström[8] found an abnormally anterior position of the anterior tricuspid leaflet in his patients with Ebstein's malformation and considered this to be specific and diagnostic. We could not confirm this observation in our patients; this may be explained by a different transducer position.

Like Farooki *et al.*,[12] we were unable to confirm the diagnostic value of an anterior tricuspid leaflet amplitude twice that of the anterior mitral leaflet, or an increased closing slope of the anterior tricuspid leaflet.[6]

Lundström[8 15] and Farooki *et al.*[12] observed a delayed or (in a few cases) simultaneous opening of the anterior tricuspid leaflet (point Td) relative to opening of the anterior mitral leaflet. Three of our patients (Fig. 4) showed a negative MdTd (–0·2 to –0·06 s); however, in all these three cases McTc was prolonged (0·09 to 0·11 s). If one ignores the difficulty in locating the point 'd' precisely in certain cases, these observations reflect the variable anatomical and echocardiographic features of Ebstein's anomaly.

In patients with Ebstein's malformation normal or abnormal septal movement may be found.[8 10 12] The relation between the sizes of the right and left ventricles seems to be important in this context. All our patients showed a paradoxical septal movement type A and in all cases the right ventricular diameter was larger than the diameter of the left ventricle. One of our patients showed mitral valve prolapse on the left ventriculogram. To our knowledge, this has been reported previously in only seven cases with Ebstein's anomaly.[19 20] The diagnosis of mitral valve prolapse is difficult in this disease because the murmur of tricuspid regurgitation and the split first heart sound of Ebstein's anomaly mask the typical auscultatory findings of mitral prolapse; moreover, in these cases the mitral valve apparatus is sometimes difficult to record echocardiographically, and during cardiac catheterisation left ventriculography is seldom performed.

Our findings and those recorded in earlier published reports show that Ebstein's anomaly can be diagnosed by echocardiography in many cases. Simultaneous recording of the tricuspid and mitral valves with a transducer position outside the left midclavicular line may be a clue to the diagnosis, and a tricuspid closure delay of 0·065 s and more may be considered as diagnostic, since exceptions are very rare. Our results support the view that echocardiography, with clinical examination, makes it possible to avoid the relatively high risk of cardiac catheterisation in Ebstein's anomaly, particularly in those patients with mild or severe forms of the disease for whom surgical treatment is not being considered.

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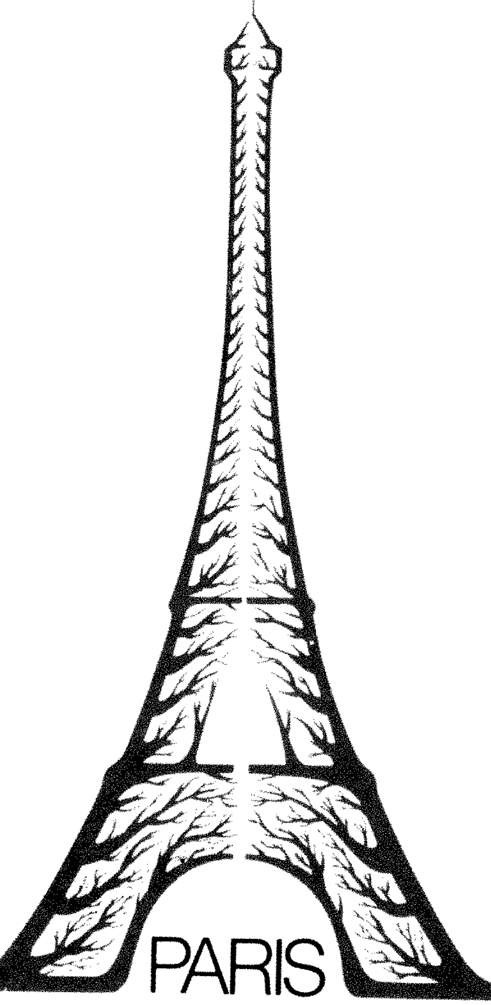

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Br Heart J 1980; **43**: 45–46

Echocardiography and rupture of the heart

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SUMMARY In four patients with rupture of the free wall of the left ventricle, the diagnosis was made at the bedside using a portable cross-sectional echocardiograph; this was confirmed at necropsy in two patients and by paracentesis in the other two.

Weak ventricular contractions were seen after each QRS complex of the electrocardiogram, contradicting a widespread belief that cardiac rupture immediately produces electromechanical dissociation. In one patient aspiration of 100 ml blood from the pericardium allowed resumption of cardiac pump function; this patient survived for three days but was allowed to die because of cerebral damage sustained during resuscitation.

Rupture of the free wall of the left ventricle is usually unheralded, occurring in one to five per cent of all myocardial infarctions; at present this represents 20 per cent of in-hospital mortality for these patients.[1–3]

The clinical diagnosis of acute cardiac rupture is suggested by the absence of pulse and heart sounds despite a normal electrocardiographic monitoring lead.[4]

During the past few months we used echocardiography at the bedside in four patients with cardiac rupture. The instrument (Minivisor, Organon Technika) is a mushroom-shaped, portable, battery-powered, linear array echocardiograph which displays a 10×20 cm cross-section of the heart on a 2×4 cm oscilloscope[5] but does not make graphic recordings.

Case reports

CASE 1

A 66-year-old man suddenly became comatose three days after an acute transmural anterior myocardial infarction. The pulse could not be felt even in the carotid arteries, yet electrocardiographic monitoring showed normal sinus rhythm. Immediate echocardiographic examination showed that the long axis cross-section of the heart was surrounded by a characteristic horseshoe-shaped contour of echo-free pericardial effusion[6]; the left ventricle was very dilated, and each QRS complex of the electrocardiogram was associated with hypokinetic cardiac contractions. Blood was present in the pericardium. This patient was prounced dead after five minutes of attempted resuscitation (wide fixed pupils and electrocardiographic as well as echocardiographic cardiac standstill). Necropsy was refused by the family.

CASE 2

A 58-year-old man experienced chest discomfort on the fifth day after an uncomplicated transmural diaphragmatic myocardial infarction; 10 minutes later he suddenly lost consciousness. Weak carotid and femoral pulses could be felt for 45 minutes. Echocardiography showed a dilated left ventricle and left atrium with hypokinetic movements of the posterior wall of the left ventricle and no movements of the interventricular septum. The cardiac silhouette was surrounded by a horseshoe-shaped crescent of echo-free pericardial fluid; pericardiocentesis disclosed unclotted blood. Despite continued attempts at resuscitation, the carotid pulses disappeared five minutes before the onset of an agonal rhythm on the electrocardiographic monitor. At necropsy, a cardiac tear was found at the border of the transmural infarct, with 250 ml blood in the pericardial sack.

CASE 3

A 75-year-old man sustained pulmonary oedema and ventricular fibrillation shortly after the onset of acute diaphragmatic infarction; resuscitation was

Received for publication 11 June 1979

successful. On the second day he complained of chest pain which responded well to glyceryl trinitrate. On the third day he experienced epigastric pain, and 30 minutes later developed pulmonary oedema and ventricular fibrillation. Defibrillation restored sinus rhythm but not blood pressure. Echocardiography showed pericardial effusion and movements of the mitral valve associated with each QRS complex. Pericardial puncture showed unclotted blood at a depth of 3 cm from the skin surface; 100 ml blood was aspirated from the pericardium, and, progressively, the blood pressure reappeared, diuresis resumed, and peripheral circulation reverted to normal. At that time, the echo-free horseshoe-shaped pericardial effusion had disappeared, the left ventricle was enlarged with good contractions of the interventricular septum; the posterior wall of the left ventricle was poorly visualised and appeared akinetic. Unfortunately, brain damage occurred during the lengthy resuscitation procedure (one hour before normalisation of blood pressure) and the patient died four days later. Necropsy was refused by the family.

CASE 4

A 73-year-old man was recovering well from a lateral myocardial infarction when, on the sixth day after his infarct, he suddenly collapsed on the ward. Resuscitation was initiated within 30 seconds; the electrocardiogram showed slow sinus rhythm but the carotid pulse was impalpable. Echocardiography showed an enlarged left ventricle with weak contractions of the ventricular walls and movements of the anterior mitral valve leaflet; there was a horseshoe-shaped crescent of pericardial effusion. Resuscitation failed and the patient was pronounced dead 30 minutes later. Necropsy showed obstruction of the left circumflex artery with a recent lateral myocardial infarction, a tear through the infarcted area, and 300 ml blood in the pericardium.

Discussion

Only immediate cardiac surgery with repair of the tear in the free wall of the left ventricle is likely to save the life of patients with rupture of the heart.[2] Few interventions have been successful in cardiac rupture,[7-9] but O'Rourke[10] reported a more favourable outcome when an early diagnosis was made. However, cardiac surgery is hazardous soon after an acute myocardial infarction, so this risk is acceptable only if the diagnosis of cardiac rupture is certain. This certainty can be provided within 30 seconds by means of a portable cross-sectional echocardiograph.

The absence of pulse and heart sounds despite normal sinus rhythm on the electrocardiogram has suggested that cardiac rupture after acute myocardial infarction produces tamponade and electromechanical dissociation. Cross-sectional echocardiography showed that each QRS complex was associated with weak contractions of the non-infarcted walls of the heart, even after the onset of an agonal rhythm. Electromechanical coupling is still present in these patients, even though the resulting movements of the left ventricular walls produce no palpable peripheral pulses.

Aspiration of 100 ml pericardial blood was associated with a resumption of cardiac pump function in one patient. One wonders whether invasive resuscitation might save some patients with a ruptured left ventricle.

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Requests for reprints to Dr F Hagemeijer, Sint Franciscus Gasthuis, Kleiweg 500, 3045 PM Rotterdam, The Netherlands.

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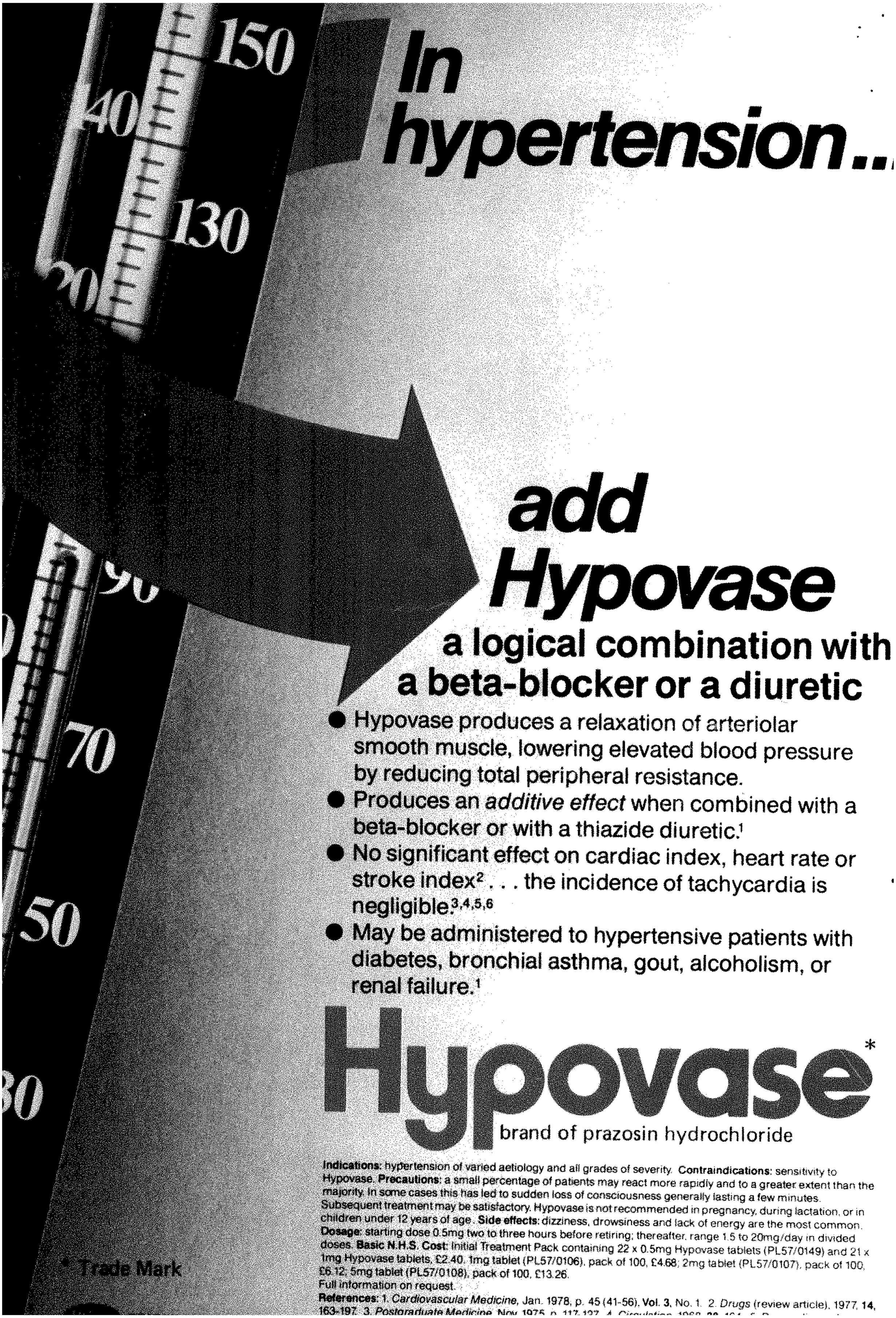

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Full information on request.

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Br Heart J 1980; **43:** 47–55

Functional significance of coronary collateral circulation during dynamic exercise evaluated by thallium-201 myocardial scintigraphy

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SUMMARY Sixty-five patients with angiographically documented coronary artery disease were investigated by thallium-201 (^{201}Tl) scintigraphy to determine the role of the collateral circulation during dynamic exercise. Fifty-three patients had complete proximal occlusion of at least one major coronary artery. One patient had total occlusion of all three major coronary arteries. Sixty-four collateral channels were identified, graded, and compared with corresponding regions of the myocardial scintigram. Tracer uptake was also graded and classified as various degrees of protection from ischaemia.

A significant correlation between good collaterals with complete protection and poor or absent collaterals with no protection was noted.

Seventeen patients (20 occluded vessels) had total coronary occlusion without myocardial infarction. Collaterals conferred protection in 9/15 occlusions whereas no protection was seen in five occlusions without collaterals.

There was no difference in the protective role of homocoronary and heterocoronary collateral vessels. Hypertrophy of the first septal left anterior descending perforator conferred significant protection from ischaemia in contrast to bridging collaterals and ghosting.

During exercise the right coronary bed is preferentially protected from ischaemia, in contrast to the left anterior descending territory. This probably reflects the direction of a transmural flow gradient between left and right ventricles during exercise.

Controversy concerning the functional significance of the coronary collateral circulation in man has been compounded rather than resolved since the introduction of selective coronary arteriography despite the excellent in vivo description of collateral vessels given by several authors using this technique.[1–3] Perhaps debate is inevitable when no reference method exists for determining collateral flow in man and observations are drawn from indirect measurement. However, two factors deserve emphasis when the protective role of intercoronary anastomoses is considered.

(1) Selection of patients and experimental design. Patients with severe coronary artery disease may be excluded from analysis in two important ways; they may remain undetected and symptom free as a result of well-functioning coronary collaterals, or they may die because of inadequate development of coronary collateral vessels.

In addition to this inevitable preselection, false comparisons are frequently made between other patients. Thus, patients with coronary collaterals have worse disease than those without, but comparison between these groups should properly be based on equally severe coronary disease. Unfortunately, 'equally severe coronary disease' determined by arteriography does not necessarily indicate equivalent degrees of myocardial ischaemia. The investigator may achieve more homogeneity in selecting severe disease by studying patients with at least complete occlusion of one major coronary artery rather than accept patients with patent and less severely diseased coronary vessels as did Helfant.[4]

(2) Inappropriate methodology. Although coronary arteriography provides clear definition of significant disease in proximal coronary arteries it is less satisfactory in the delineation of coronary collateral vessels for it reveals only epicardial anastomoses of a size no smaller than 100 to 200 μ

Received for publication 22 February 1979

and not the deeper connections which exist within the myocardium.[5] Moreover, the demonstration that coronary collaterals can be filled with contrast medium does not guarantee their function, despite the claim by Frick *et al.*[6] that only collaterals carrying flow are visualised during selective arteriography, always provided that contrast medium is not forced under pressure into the coronary tree.

Myocardial imaging using thallium-201 (^{201}Tl) is a non-invasive technique which is valuable in the analysis of regional myocardial perfusion.[7] Regions of ischaemia caused by severe coronary disease appear as functional defects of tracer accumulation in the myocardial scintigram.[8] Using ^{201}Tl imaging, we have analysed the role of the coronary collateral circulation in the preservation of regional myocardial perfusion during angina pectoris induced by dynamic exercise and have identified the angiographic features of collateral vessels responsible for such protection.

Patients and methods

Sixty-five patients (62 men and three women; mean age 50 years; range 27 to 65 years) with angina pectoris were investigated by ^{201}Tl myocardial scintigraphy shortly after coronary artery disease had been demonstrated by contrast arteriography.

All patients selected for myocardial imaging had severe stenosis or total occlusion of at least one major coronary artery. The majority of patients had complete occlusion of at least one vessel and were homogeneous in this respect. A significant coronary stenosis was defined as reduction of the coronary lumen by more than 50 per cent, and severe stenosis as a reduction in diameter greater than 80 per cent. Selective coronary arteriography was performed in multiple projections using either the Sones or Judkins technique. All patients had a complete physical examination, resting 12 lead electrocardiogram, and an electrocardiogram recorded during a maximal exercise test on a Monark bicycle ergometer with lead V5 monitoring.

Subjects with hypertension, valvular heart disease, or primary myocardial disease were excluded from this study. Drugs for heart disease, particularly beta-blockers, were withdrawn before contrast angiography and myocardial scintigraphy.

During the exercise test each patient received 1·5 mCi of ^{201}Tl through an indwelling intravenous cannula at the onset of angina pectoris or limiting dyspnoea. The exercise end-point was maintained for one and a half to two minutes so that there was maximal myocardial uptake of circulating tracer in the presence of symptoms.

After a 10-minute recovery period, myocardial imaging was performed with subjects in the supine position using an Ohio-Nuclear Series 100 scintillation camera and a high-sensitivity parallel-hole collimator (Fig. 1). Anterior, left anterior oblique 45° and 55°, and full left lateral projections were routinely acquired in every patient. In each image 200 000 counts were collected using a 20 per cent window centred on the 72·5 keV mercury *x*-ray peak emitted from ^{201}Tl decay. During acquisition of the scintigrams activity from background organs such as the liver and lungs was reduced by surrounding the heart with an annulus of lead cape positioned over the praecordium beneath the gamma camera. Each image was acquired on transparency film in

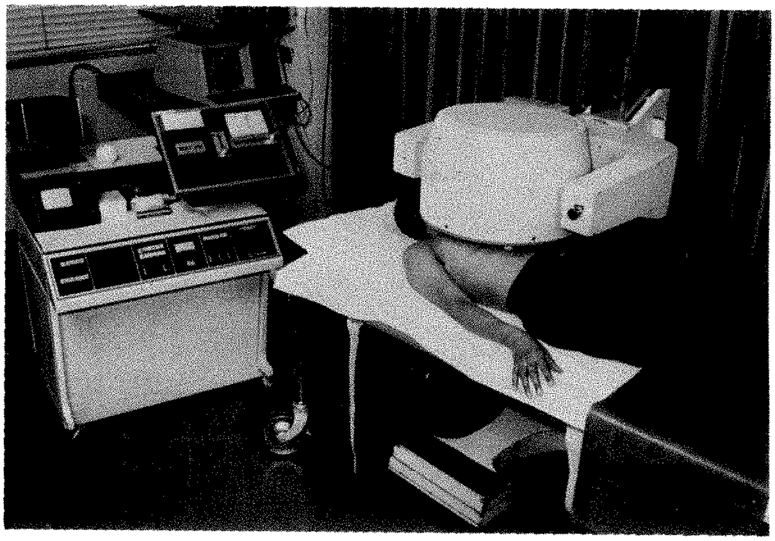

Fig. 1 *Myocardial imaging of patient at rest shortly after ^{201}Tl was administered during maximal exercise. Scintillation camera is closely apposed to praecordium while anterior scintigram is acquired. Computer terminal seen in far background links camera to dedicated minicomputer not shown.*

four to eight minutes and simultaneously stored in a 64 × 64 matrix on a magnetic disc using a dedicated minicomputer (DEC Gamma II) interfaced to the gamma camera. The digital images were enhanced by a 50 per cent background erase, interpolated and displayed on a TV monitor in 16 grades of colour which were linearly related to image intensity.

Analysis was performed by dividing the scintigram into seven roughly equal segments around its circumference using a light marker controlled by a joy-stick at the computer console. These segments were expressed as average counts per digital matrix element and compared with a normal myocardial profile previously established in our laboratory from ^{201}Tl scintigrams obtained in a group of patients without evidence of heart disease. Segments falling below the established normal range were regarded as myocardial defects.

Each defect was further classified as moderate or severe according to the degree of tracer deficit seen in that region. Moderate defects were defined as a regional reduction in count rate of 50 to 80 per cent and were identified in the colour image as areas containing a predominance of orange or red. This appearance was considered to represent partial protection from ischaemia if it occurred in an area subtended by severe coronary artery disease. A severe uptake defect was defined as a reduction in regional count rate greater than 80 per cent and appeared as a blue or black region in the colour display of the image. These defects were regarded as showing no protection from ischaemia if they were caused by severe coronary artery disease. Normal tracer uptake in regions of the scintigram supplied by severely diseased coronary arteries was regarded as complete protection from ischaemia and appeared as regions of yellow in the colour display image. Fig. 2 shows examples of these appearances.

All scintigrams were reviewed independently by two observers without knowledge of the coronary anatomy and compared with the quantitative segmental analysis. Excellent agreement was found between the two methods ($>90\%$) and inter-observer agreement was similarly high. Observer disagreements were resolved by subsequent review and consensus, calling on a third observer if necessary.

All coronary arteriograms were reviewed independently by two observers in ignorance of the scintigraphic analysis, and note was made of the site and number of complete coronary occlusions and severe coronary stenoses together with any associated coronary collateral channels.

Coronary collateral vessels were divided angiographically into two main types: (a) predominantly single channels opacified by contrast medium injected into a homolateral or contralateral coronary artery, filling via visible or invisible feeding conduits and joining the distal portion of arteries affected by severe proximal coronary disease; (b) visible or invisible 'bridging' collaterals which connect the dislocated ends of a major coronary artery through which the distal segment of the vessel was opacified after injection of contrast medium into the proximal segment.

In addition 'ghosting' of coronary vessels was noted, that is severely delayed anterograde filling and faint opacification of a distal coronary vessel after injection of contrast medium into its proximal portion.

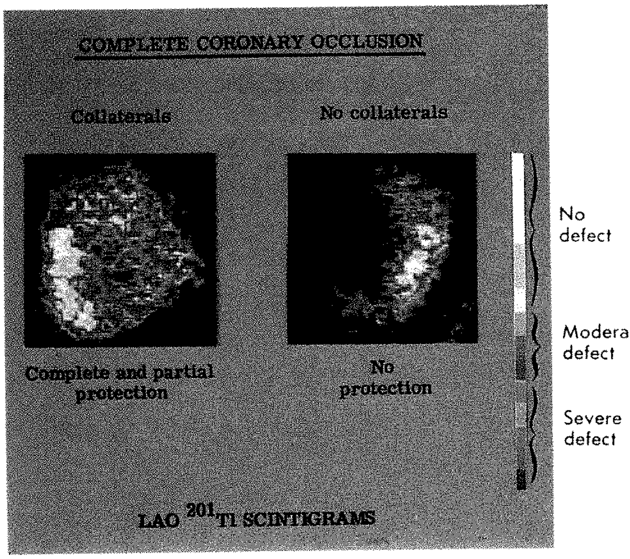
COMPLETE CORONARY OCCLUSION
Collaterals
No collaterals
Complete and partial protection
No protection
LAO ^{201}Tl SCINTIGRAMS
No defect
Moderate defect
Severe defect

Fig. 2 *Left anterior oblique 45° exercise* ^{201}*Tl scintigrams. Normal uptake of tracer in septum (IVS) with moderate but extensive defect in inferior wall (IW) and posterolateral wall (PLW) seen in patient with complete occlusion of all three major coronary arteries* (left). *IVS is yellow indicating complete protection from ischaemia whereas IW and PLW are orange-red signifying partial protection from ischaemia.*

Severe defects are seen in IVS and IW in scintigram (right). *IVS is black and IW blue indicating no protection from ischaemia.*

Sixteen grade colour table displayed (far right) *with top of scale corresponding to regions of maximal count rate.*

Heterocoronary and homocoronary collateral vessels were graded angiographically on a five-point ordinal scale according to their promptness and intensity of opacification with contrast medium.

Grade 0: absence of collateral vessels
Grade 1: poorly developed collateral vessels with no prominent distal channel visualised
Grade 2: moderate collaterals giving faint but delayed opacification of a prominent distal channel
Grade 3: good collaterals giving clear opacification of a prominent distal channel
Grade 4: excellent collaterals giving full and brisk opacification of prominent distal vessels.

Agreement between observers was excellent. Of allotted grades, 75 per cent were identical and 92 per cent differed by no more than one category in the scale. No assessment differed by more than two grades and the small number of classifications which differed by more than one grade was resolved by combined review and consensus.

Statistical comparison of data was performed using the χ^2 test corrected for continuity and the Fisher exact test.

Results

In the 65 patients studied, 110 coronary lesions were classified as angiographically severe and therefore liable to provoke the growth of collateral vessels. There were no significant lesions in the left main coronary artery. Though the majority of patients (85%) had developed at least one collateral network at the time of investigation, the observed number of collateral channels in relation to the number of coronary lesions expected to produce collateral development was only 64/110 (58%). The proportion of collateral channels for each severe coronary lesion showed a highly significant reduction ($P < 0{\cdot}005$) as single vessel disease progressed to quadruple vessel disease despite the proportion of totally occluded coronary arteries remaining constant in each group (Table 1). This observation suggests that an important factor for the development of adequate collateral growth in response to severe coronary disease and myocardial hypoxia may be an uncompromised blood supply from a healthy donor vessel.

Complete occlusion of at least one major coronary artery was seen in 53 patients: 68 occluded vessels were found in these patients and the prevalence of collateral channels was 78 per cent (Table 2). The right coronary artery was the vessel occluded most commonly (50% of all occlusions) and was also the most frequent recipient of a collateral vessel.

One patient had total proximal occlusion of all three major coronary arteries with no historical or electrocardiographic evidence of myocardial infarction and preservation of excellent left ventricular function. Indeed, a normal resting electrocardiogram, despite total proximal occlusion of at least one large coronary artery, was found relatively often, occurring in 18/65 (28%) patients in this study. Twelve patients had at least one severe coronary lesion without complete occlusion of a vessel. The prevalence of coronary collateral channels in this group was similar to that in patients with complete coronary occlusion.

MYOCARDIAL INFARCTION

Fig. 3 summarises the relation between myocardial infarction and the presence of coronary collaterals. Thirty-nine myocardial infarctions (37 transmural infarcts and two anterior subendocardial infarcts) were documented in 37 patients, an overall prevalence of 39/65 (60%).

There was no significant difference in the prevalance of coronary collaterals between patients who had sustained anterior myocardial infarction compared with patients with inferior myocardial infarction. Similarly, there was no difference in the frequency of coronary collateral development between patients with myocardial infarction and those without infarction.

Table 1 *Distribution of occluded arteries and corresponding collateral vessels in patients with severe coronary artery disease*

No. of vessels with significant disease (stenosis > 50%)	*No. of patients*	*No. of patients with at least one collateral bed*	*Total no. of collateral beds*	*Total no. of occluded vessels*	*Total no. of severe lesions (stenosis > 80%)*	*Proportion of collateral beds per severe lesion*	*Proportion of occluded vessels per severe lesion*	*Proportion of collateral beds associated with occluded vessels*
Single	13	9	9	7	13	0·69	0·54	0·62
Double	21	21	27	22	32	0·84	0·69	0·90
Triple	26	21	34	31	52	0·65	0·60	0·62
Quadruple	5	4	4	8	13	0·31*	0·62	0·60
Total	65	55	64	68	110			

* $P < 0{\cdot}0005$.

Individual coronary arteries and their collateral supply

Left anterior descending collaterals. No patient with left anterior descending collaterals of any category had complete protection from the appearance of exercise-induced uptake defects in the ^{201}Tl scintigram, though seven patients did exhibit varying degrees of partial protection. Only one patient in the partially protected group had poor development of collateral vessels compared with 19 patients in the group with no protection ($P < 0{\cdot}01$) (Fig. 4). Hypertrophy of the first septal perforating artery was included in the analysis of left anterior descending collaterals and classified angiographically as a grade 3 (good) collateral vessel in view of its large calibre lumen and rapid filling. Enlargement of this vessel appeared to provide significant protection from ischaemia in the septal distribution of the left anterior descending. Four of seven patients in the group with partial left anterior descending uptake defects had hypertrophy of the first septal perforator compared with only one of 27 patients in the group with no protection as seen on the scintigram ($P = 0{\cdot}003$).

Right coronary artery collaterals. All three grades of scintigraphic protection were seen in patients with right coronary artery collaterals (Fig. 5). Twelve patients with total proximal occlusion (10 patients) or severe stenosis (two patients) of a dominant right coronary artery had complete protection from ischaemia as shown by completely normal myocardial uptake of ^{201}Tl in the distribution of this vessel. It was surprising to see this degree of protection in the presence of extensive disease in other coronary vessels, for example nine patients had severe triple vessel disease while the artery donating collaterals to the right coronary artery had significant disease in 11 patients.

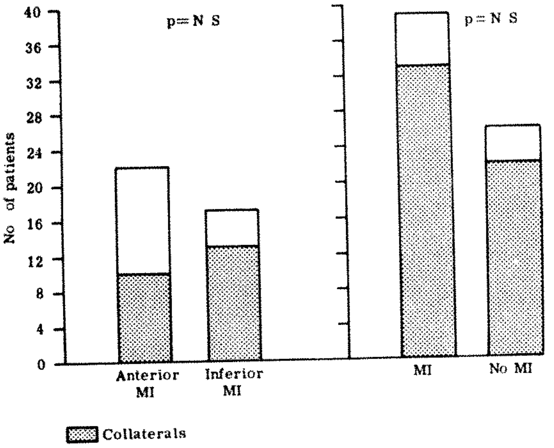

Fig. 3 *Prevalence of coronary collaterals was not significantly different in patients with anterior and inferior myocardial infarction* (left), *nor was there significant difference in prevalence of collaterals between patients with myocardial infarction and patients without myocardial infarction* (right).

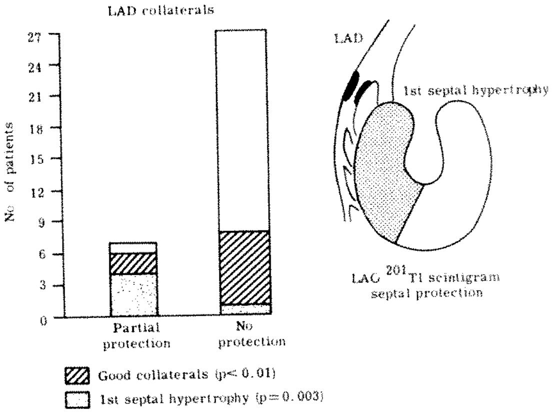

Fig. 4 *Patients with severe left anterior descending disease and partial protection in corresponding regions of scintigram have higher prevalence of adequate collateral channels than patients with no scintigraphic protection. Most patients have no protection despite presence of collaterals. No patient has complete protection. Hypertrophy of first septal perforator is significant factor in preservation of septal tracer uptake.*

The prevalence of collaterals allotted grade 3 or more was highest in patients with complete protection in the scintigram and fell with decreasing degrees of protection, though these figures did not achieve statistical significance ($P > 0{\cdot}5$). No patient with complete protection had absent collateral development in contrast to four patients with partial or no protection who had no collateral channels visible on angiography.

In six patients with no scintigraphic protection, four had sustained inferior myocardial infarction despite visualisation of good collaterals to the right coronary artery in three. Eight inferior myocardial infarctions were found in the partially protected group while no patient with myocardial infarction was seen in the group with complete protection ($P < 0{\cdot}1$).

Left circumflex collaterals. Left circumflex coronary lesions were not often associated with prominent retrograde collateral filling though there was often angiographic 'ghosting' of the distal bed. Fig. 6 shows that the majority of patients with severe left circumflex coronary lesions had no protection from the appearance of uptake defects in the myocardial scintigram seen in the distribution of this vessel. No patient with this lack of protection had adequate development of collateral channels, whereas three patients with partial protection had moderately good collateral growth. One patient with excellent retrograde visualisation of the whole left circumflex artery had entirely normal tracer uptake in the distribution of this vessel. Thus, poor collaterals and ghosting of the left circumflex territory were significantly associated with prominent uptake defects in the ^{201}Tl myocardial scintigram and did not confer protection ($P=0\cdot05$).

The influence of coronary collateral channels on the myocardial uptake of ^{201}Tl may be demonstrated more clearly by examining only regions of ischaemia and excluding regions of necrosis, for myocardial infarction causes permanent defects of ^{201}Tl accumulation which cannot be attenuated by subsequent revascularisation.

PATIENTS WITH CORONARY OCCLUSION WITHOUT MYOCARDIAL INFARCTION

Only 17 patients had no historical or electrocardiographic evidence of myocardial infarction and total occlusion of at least one major coronary artery. The scintigrams of these patients were correlated with the appearance of corresponding coronary collateral vessels seen on angiography. Twenty occluded coronary vessels were found in this group of patients, most of whom had one artery completely occluded and significant disease in other vessels. Six patients had left anterior descending artery occlusion, seven patients had right coronary artery occlusion, and two patients had left circumflex artery occlusion. One patient had two vessels completely occluded and another patient had all three coronary arteries occluded without myocardial infarction.

Fig. 7 shows that the presence of collateral vessels confers significant protection against the appearance of exercise-induced ischaemic defects in the ^{201}Tl scintigram. In the presence of collaterals nine of 15 ischaemic vascular beds were associated with mild or no uptake defects whereas all five vascular beds (two left anterior descending and three left circumflex) without a collateral circulation were readily identified as stark defects appearing in corresponding regions of the scintigram ($P=0\cdot03$). There was no significant difference in the prevalence of severe coronary disease between these groups nor was there any significant difference in the total exercise achieved by the time ^{201}Tl was administered (3385 kpm v 3130 kpm, NS).

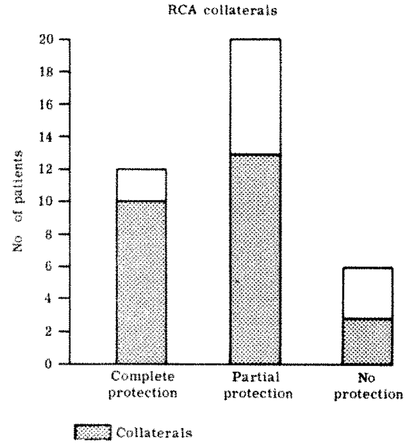

Fig. 5 *Twelve patients have normal uptake of ^{201}Tl (complete protection) in distribution of right coronary artery despite severe occlusive disease in this vessel. Ten of these patients have excellent development of coronary collateral vessels though there is no significant difference in prevalance of collaterals among degrees of protection.*

PATIENTS WITH OCCLUSION OF TWO CORONARY ARTERIES

Patients with double coronary artery occlusion were of interest in the functional interpretation of dual collateral beds. Retrograde opacification of the distal segment of each occluded vessel after injection of contrast medium into the proximal segment of a diseased donor artery was commonly seen under the artificial pressure gradients produced in the coronary tree at the time of angiography. No information is provided by arteriography about the direction of collateral flow during angina pectoris induced by exercise.

Combined occlusion of the right coronary artery and left anterior descending artery was found in nine out of 13 patients. Anterior myocardial infarction was no more frequent than inferior myocardial infarction in these patients nor was there a difference in the prevalence of coronary

Table 2 *Prevalence of collateral vessels in patients with total occlusion of at least one coronary artery*

No. of occluded vessels per patient	*No. of patients*	*Total no. of collateral beds*	*Total no. of occluded vessels*	*No. of collateral beds per occluded vessel*		
				RCA	*LAD*	*LCx*
1	39	29	39	17	9	3
2	13	22	26	11	8	3
3	1	2	3	1	1	0
Total	53	53	68	29	18	6

RCA, right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery.

collateral channels feeding the distal bed of either the right coronary artery or left anterior descending artery. However, there was a distinct difference in the pattern of scintigraphic uptake defects produced by these two occluded vessels.

Right coronary artery occlusion was associated with significantly less severe uptake defects in the myocardial scintigram than was total occlusion of the left anterior descending ($P < 0{\cdot}05$) (Table 3). Thus, during maximal dynamic exercise the collateral circulation to the right coronary bed maintained a delivery and distribution of ^{201}Tl sufficient to prevent uptake defects appearing in this region of the scintigram. In contrast, little protective effect could be shown for collaterals supplying the distal left anterior descending, for uptake defects regularly appeared in the distribution of this artery at the limiting end-point of exercise. Defects attributable to right coronary artery disease were never seen in the absence of defects resulting from left anterior descending disease, that is the left anterior descending artery was probably always responsible for producing angina with this combination of coronary occlusions.

A similar situation was seen in patients with combined right coronary artery and left circumflex coronary artery occlusion. Myocardial uptake defects were always seen in the distribution of the left circumflex vessel whereas partial defects or no uptake defects at all occurred in the distribution of the right coronary artery.

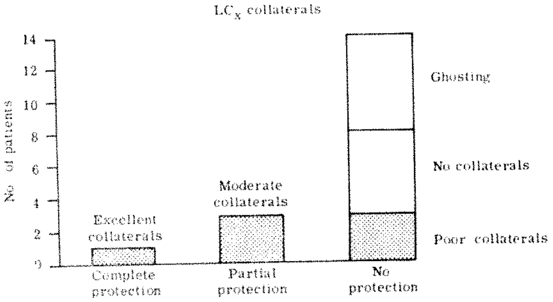

Fig. 6 *Most patients with severe disease in left circumflex coronary artery have no protection from ischaemia; in particular, angiographic ghosting and absent collaterals are always accompanied by severe uptake defects in scintigram (no protection). Three patients with moderate collateral development have partial protection from ischaemia and one patient with excellent collateral vessels has complete protection.*

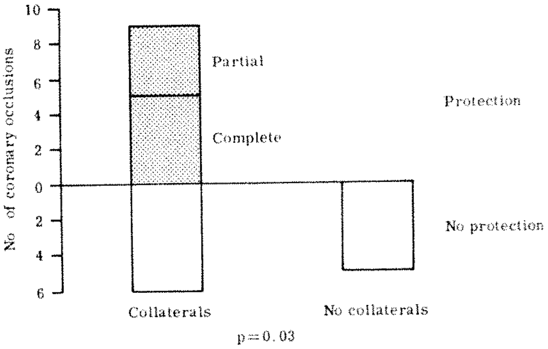

Fig. 7 *Collateral development and accompanying protection from ischaemia seen in patients with complete occlusion of at least one vessel but no evidence of myocardial infarction. Protection was never seen in absence of coronary collateral channels.*

Only one patient had combined left anterior descending and left circumflex coronary occlusions both of which were apparent in the scintigram, there being a poor collateral supply to each vessel.

CORRELATION OF COLLATERALS WITH ^{201}TL MYOCARDIAL UPTAKE

Fig. 8 shows the relation between the degree of coronary collateral development assessed angiographically and the severity of ^{201}Tl uptake defects seen in the myocardial scintigram. There was a highly significant association between well-developed coronary collateral vessels and accompanying preservation of myocardial ^{201}Tl uptake. Similarly, poor or absent coronary collateral development was usually associated with severe deficit of tracer in corresponding regions of the scintigram ($P < 0{\cdot}0005$, coefficient of contingency $= 0{\cdot}50$).

There was no significant difference in the

Table 3 *Prevalence of collateral vessels in patients with complete occlusion of two coronary arteries*

Combinations of coronary artery occlusion	*No. of patients*	*No. of collateral beds*			*No. of corresponding protected areas in scintigram*		
		RCA	*LAD*	*LCx*	*RCA*	*LAD*	*LCx*
RCA and LAD	9	8	8	—	7*	4	—
RCA and LCx	3	3	—	0	2	—	0
LAD and LCx	1	—	1	0	—	0	0

* $P < 0{\cdot}005$ for difference in severity between uptake defects found in right coronary artery and left anterior descending artery territories.
RCA, right coronary artery; LAD, left anterior descending artery; LCx, left circumflex artery.

protective effect of homocoronary and heterocoronary collateral vessels independent of their degree of development. Angiographically invisible coronary collaterals were never associated with complete scintigraphic protection and usually conferred no protective benefit. Similarly, vessel ghosting was always accompanied by severe scintigraphic uptake defects. Bridging collaterals also offered inadequate protection from myocardial ischaemia during exercise, but hypertrophy of the first septal perforating artery did appear to offer significant protection to the septum in the presence of severe left anterior descending disease.

Discussion

The advent of coronary artery bypass graft surgery has brought renewed interest in the coronary collateral circulation and its functional significance, for the chances of successful graft patency are enhanced if the distal segment of an occluded artery has good flow maintained by collateral vessels. Some patients may have sufficient collateral flow to render this operation superfluous though the early study of Blumgart[9] suggests that collaterals are adequate only at rest. This finding is supported by Helfant and colleagues[4] who noted that abnormal myocardial lactate metabolism and abnormal post-exercise electrocardiograms were even more common in patients with collateral vessels than in those without, which led the authors to conclude that coronary collateral vessels were inadequate to meet the increased myocardial oxygen demands during stress. A similar inadequacy of the collateral circulation to prevent ischaemia, as measured by a submaximal treadmill test, was found by Harris *et al.*[10]

Using ^{201}Tl myocardial scintigraphy many patients with total occlusive disease of a dominant right coronary artery are seen to have adequate collateral vessels providing complete protection from ischaemia in the distribution of this artery during dynamic exercise. Patients with left anterior descending disease, however, were not protected from the appearance of ischaemic uptake defects. Selective protection of the distal right coronary artery would neither prevent abnormal myocardial lactate metabolism nor abnormal exercise electrocardiograms in the presence of severe left anterior descending disease. Previous studies using these indirect measures of regional myocardial perfusion may have failed to detect the preferential vascular protection now described.

Although the mechanism for this protection is not clear the normal pressure gradient that exists between left and right ventricles may be increased during dynamic exercise, particularly during diastole in an ischaemic left ventricle, so that collateral flow is maintained or increased in the direction of the low pressure right ventricular myocardium. This effect probably accounts for the preservation of tracer uptake in the inferior wall of the left ventricle as seen in ^{201}Tl scintigrams. Clinical support for this concept is found in two situations: (a) right ventricular myocardial infarction is rare in man despite the frequency of total right coronary artery occlusion[11]; (b) internal mammary artery implants to the right ventricle remain patent more easily than implants to the left ventricle.[12]

Experimental support for this concept is also provided by Ramo *et al.*[13] who showed that despite similar rates of right coronary artery and left anterior descending coronary occlusion in the pig, collateral vessels to the right coronary artery developed more rapidly and more extensively than to the left anterior descending.

However, one relevant limitation of ^{201}Tl imaging is that relative regional myocardial

ANGIOGRAM

Collateral grades

SCINTIGRAM	Nil	Poor	Moderate	Good	Excellent
Complete protection			▮	▮▮▮▮▮▮	▮▮▮▮▮▮
Partial protection	▮▮▮	▮▮	▮▮▮▮▮▮▮ B	▮▮▮▮▮ ▮▮▮▮▮ ↑ ↑ ↑ ↑	▮▮▮▮▮
No protection	▮▮▮▮▮▮▮▮▮ ▮▮▮▮▮▮▮▮ B B B + + + + + + + + +	▮▮▮▮▮▮▮	▮▮▮▮	▮▮▮▮▮ ↑	▮▮▮▮

Fig. 8 *Correlation of coronary collateral development with ^{201}Tl myocardial uptake seen in corresponding regions of the scintigram.* ▮, *Homocoronary and heterocoronary collaterals; B, bridging collaterals;* ↑, *hypertrophy of first septal perforator of left anterior descending artery;* +, *ghosting.*

ischaemia is reflected in the scintigram rather than in terms of absolute perfusion. Thus, it is possible that even the right coronary artery territory is ischaemic during exercise, though better perfused than the left coronary artery.

Several conclusions remain to be drawn from these data:

(a) There is no difference between homocoronary and heterocoronary anastomoses in protection from ischaemia.

(b) Enlargement of the first septal branch of the left anterior descending appears to provide significant protection from septal ischaemia and should be regarded as an important collateral channel.

(c) In contrast to the study of Knoebel *et al.*[14] bridging collaterals did not offer any protection from the scintigraphic detection of ischaemia.

(d) Angiographic ghosting of vessels was always associated with severe uptake defects in the scintigram. Ghosting probably occurs because of previous severe occlusive disease and does not indicate a collateral channel of any functional significance.

(e) The clear correlation between the angiographic grading of collaterals and corresponding areas of protection seen in the scintigram gives the angiographer reasonable reassurance that there is functional relevance in a detailed description of these important channels. Further support for this correlation is found in the postmortem data of Spain *et al.*[15] and in the study of Scherer *et al.*[16] who compared collaterals quantified angiographically before operation with collateral flow measured during coronary artery bypass surgery.

^{201}Tl scintigraphy provides a functional map of the myocardium in terms of patterns of ischaemia and thus allows a functional interpretation of corresponding anatomy seen in the coronary arteriogram. In future it may be possible to assess non-invasively the influence of chronic interventions such as graded physical exercise and drug therapy on the time-course and development of coronary collateral vessels by monitoring changes in the ^{201}Tl scintigram.

Dr R J Wainwright was supported by a British Heart Foundation grant.

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Exercise thallium-201 myocardial scintigraphy in the follow-up of aortocoronary bypass graft surgery

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SUMMARY The predictive accuracy of exercise thallium-201 (^{201}Tl) myocardial scintigraphy in the evaluation of aortocoronary bypass graft surgery was assessed in 48 patients undergoing angiographic investigation 15 months (mean time) after myocardial revascularisation. ^{201}Tl scintigrams detected 61 out of 77 (79%) patent grafts but only 21 out of 42 (50%) occluded grafts, though, for grafts supplying non-infarcted myocardium, the predictive accuracy of graft patency and graft occlusion was 85 per cent and 81 per cent, respectively. Stress electrocardiography failed to detect 15 out of 21 patients with scintigraphic evidence of regional myocardial ischaemia. Residual ischaemia in the proximal left anterior descending coronary distribution was commonly detected in ^{201}Tl scintigrams despite a patent, well-functioning left anterior descending graft to the distal coronary segment. Additional residual ischaemia attributable to ungrafted coronary disease was detected by scintigraphy in 32 (67%) patients and most commonly occurred in the distribution of the diagonal branch of the left anterior descending especially in the presence of a patent distal left anterior descending graft. Thus, independent grafts to the diagonal branch of the left anterior descending are recommended at the time of aortocoronary bypass graft surgery.

After aortocoronary bypass graft surgery approximately 20 per cent of patients may need investigation with coronary and graft arteriography to evaluate persistent or recurrent chest pain often not typical of angina pectoris. Though freedom from angina after surgery is positively correlated with vein graft patency[1 2] it does not follow that recurrent angina is always caused by vein graft occlusion, for Di Luzio *et al.*[3] found that patients with occluded grafts may also be free from pain. Thus, chest pain after coronary bypass graft surgery must sometimes depend upon factors other than graft occlusion, including:

(a) progression of native coronary disease in grafted and ungrafted vessels;
(b) functional inadequacy of patent grafts caused by graft stenosis or poor graft run-off;
(c) deterioration of left ventricular function.

In addition, chest pain not directly related to the vascular status of myocardium (for example, non-union of the sternum) may resemble angina pectoris and provoke unnecessary arteriography.

A minimally invasive technique, such as exercise thallium-201 (^{201}Tl) myocardial scintigraphy, which could sensitively distinguish regions of persistent myocardial ischaemia from necrotic and normal myocardium,[4 5] would be a valuable asset in the preliminary analysis of patients with chest pain after coronary artery surgery, as those patients in whom regional myocardial ischaemia could not be demonstrated might be precluded from further invasive investigation.

This study had two objectives: firstly, to correlate postoperative coronary and graft arteriograms with exercise ^{201}Tl myocardial scintigrams in patients with previous aortocoronary bypass surgery in order to define scintigraphic criteria which could be used to predict the status of individual coronary bypass grafts; secondly, to analyse the contributions of revascularisation and necrosis to the mechanism of pain relief after surgical revascularisation of the myocardium.

Patients and methods

Forty-eight patients (44 men and four women; mean age 51, age range 32 to 64 years) who had previous aortocoronary saphenous vein graft surgery were reinvestigated by selective coronary and graft arteriography. Eighteen patients had typical angina pectoris closely resembling their preoperative pain (group A), 13 patients had praecordial pain considered atypical of angina pectoris but which also resembled their preoperative pain (group B), and 17 patients had no chest pain at all (group C).

Received for publication 20 November 1978

In the latter group, 10 patients were completely symptomless while the remainder were limited by breathlessness or undue fatigue.

Four patients had a single graft, 18 patients had two grafts, 25 patients had three grafts, and one patient had four grafts (average 2·5 grafts per patient). Forty-six grafts were placed to the left anterior descending coronary artery or its main diagonal branch, 41 to the right coronary artery, and 32 to the left circumflex vessel or its obtuse marginal branch. Autologous saphenous veins were used as grafts and anastomosed to coronary vessels with at least 50 per cent stenosis of the proximal lumen. In addition to coronary artery surgery one patient had an aneurysmectomy and one patient had an aneurysm plicated, but no other procedures, such as valve replacement, were performed.

CORONARY ARTERIOGRAPHY

Contrast cineangiography of the native and graft circulation was performed using the Sones or Judkins technique. All patent grafts were demonstrated in at least two views. Occluded grafts were recognised by selective opacification of a graft stump at the aortic anastomosis. If a graft could not be visualised by selective catheterisation a large bolus of contrast medium was rapidly injected into the aortic root. Grafts not opacified by either method were classified as 'not demonstrated' and presumed occluded. All coronary arteriograms were reviewed independently by two observers in ignorance of corresponding myocardial scintigrams. The state of the native coronary vessels and the integrity of the venous grafts were noted. Particular attention was paid to graft stenoses and whether the degree of graft run-off, assessed by the size of the distal vessels and their promptness to opacify, was adequate. Graft run-off was graded as good, moderate, or poor. Narrowing of a coronary artery or graft greater than 50 per cent of the lumen diameter was considered haemodynamically significant.

Although assessment of the arteriographic data was visual and necessarily subjective, the consensus of opinion of at least three observers was always obtained. The mean time between surgery and follow-up arteriography was 14·9 months (range six to 72 months) and the mean time between arteriography and scintigraphy was 48·6 days (range zero days to 13 months). Scintigraphy and arteriography were separated by less than a month in most patients (36).

EXERCISE MYOCARDIAL SCINTIGRAPHY

Patients were exercised in the upright position on a bicycle ergometer, monitoring the V5 lead of the electrocardiogram, until the onset of limiting symptoms. An exercise electrocardiogram was regarded positive for ischaemia if 1 mm or more ST segment depression was seen 0·08 second after the J point in three consecutive beats; 2 mCi of ^{201}Tl was given through an indwelling intravenous cannula at an exercise end-point which was maintained for approximately one-and-half to two minutes after administration of tracer. After a 10-minute recovery period myocardial imaging was performed with subjects in the supine position using an Ohio Nuclear series 100 scintillation camera and a high-sensitivity parallel-hole collimator. Four views of the myocardium were routinely acquired; viz: anterior, left anterior oblique (LAO) 45°, LAO 55°, and a full left lateral projection; 200 000 counts were collected in each image using a 20 per cent window centred on the 72·5 keV mercury x-ray peak emitted by ^{201}Tl decay. Each image was acquired in four to eight minutes on transparency film and simultaneously recorded in a 64 × 64 matrix on magnetic disc using a dedicated minicomputer (DEC Gamma II) interfaced to the gamma camera. Digital images were displayed on a TV monitor in 16 grades of colour, linearly related to image intensity, and enhanced by a 50 per cent background erase. Each image was carefully compared with a group of normal myocardial ^{201}Tl scintigrams previously acquired in our laboratory from patients without evidence of heart disease, including asymptomatic healthy normal volunteers. This comparison was facilitated by using a computer 'area-of-interest' analysis. Segmental areas of interest were outlined on the myocardial images and then expressed quantitatively as average counts per element of the digital matrix. Each segment corresponded approximately to 14 per cent of the myocardial circumference. Segments which fell below our established normal range were regarded as myocardial defects. We have found this semi-quantitative technique sensitive and reproducible; reliance solely on visual interpretation of the images is thus minimal. If necessary, patients had repeat delayed images of the myocardium performed in selected views several hours later in order to distinguish regions of severe myocardial ischaemia, which undergo reperfusion, from the fixed uptake defects of myocardial necrosis.

SCINTIGRAPHIC CRITERIA OF GRAFT INTEGRITY

The functional adequacy of venous bypass grafts, and thus, indirectly, whether grafts were likely to be patent or occluded, was determined by using the following *a priori* criteria based on the appearance

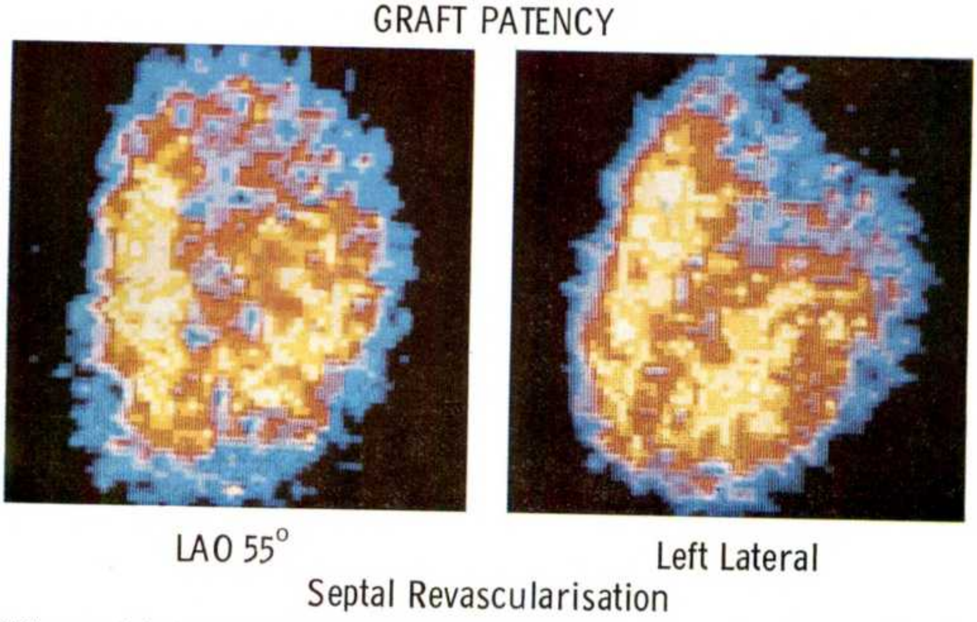


Fig. 1 ^{201}*Tl myocardial scintigram LAO 55°. Normal tracer uptake in the septum is preserved by a patent left anterior descending graft despite total proximal occlusion of the artery* (left). *Left lateral view. A separate graft to the left anterior descending diagonal branch in the same patient accounts for normal tracer uptake in the anterolateral wall* (right).

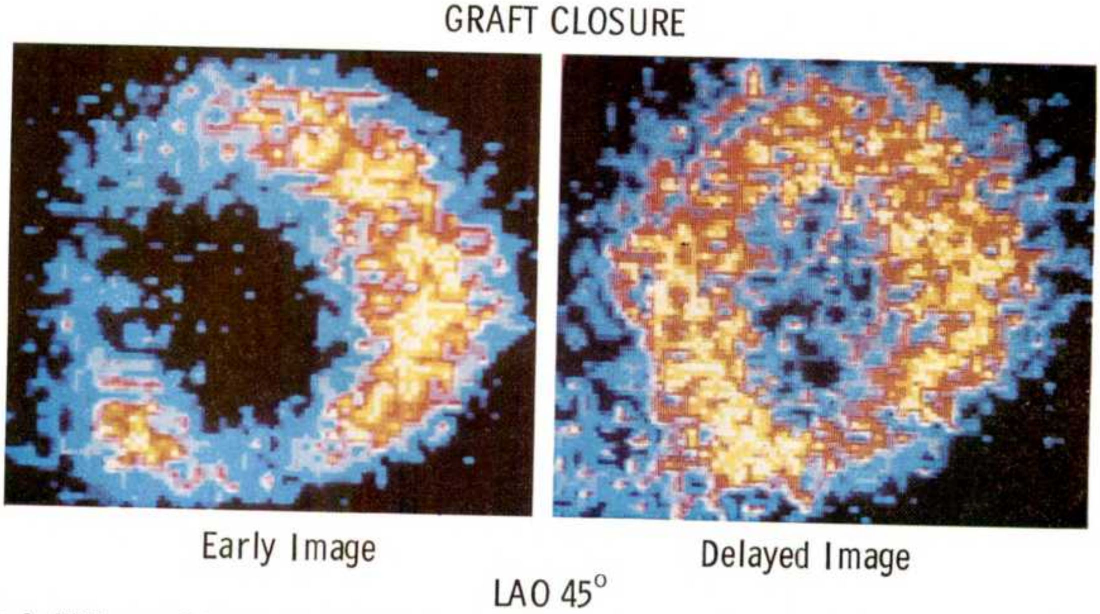


Fig. 2 ^{201}*Tl myocardial scintigram LAO 45°. A severe deficit of tracer in the septum is seen in the early post-exercise image* (left) *which is not evident in the delayed image* (right) *because of tracer redistribution. This septal ischaemia was caused by significant proximal left anterior descending disease and unrelieved by a severely stenosed but patent left anterior descending graft.*

of tracer in appropriate regions of the myocardial scintigram.

(a) Exercise-induced tracer defects resulting from severe coronary disease would not be expected to appear in corresponding regions of the ^{201}Tl scintigram if patent venous grafts provided an alternative route for tracer. Thus, the absence of a tracer defect in the territory of a previously grafted coronary artery with severe proximal disease is regarded in this study as a scintigraphic indication of graft patency (Fig. 1).

(b) Conversely, venous grafts which are stenosed, occluded, or have poor run-off will allow underlying coronary disease to cause ischaemic tracer defects in the myocardial scintigram. Thus, tracer deficit in the territory of a previously grafted, severely diseased coronary artery is regarded as a sign of graft insufficiency (Fig. 2). Clearly, the anatomical pathology of functionally inadequate grafts cannot be distinguished by myocardial scintigraphy alone but must be determined by graft angiography.

(c) Finally, judgement cannot be made about graft integrity if a graft subtends necrotic myocardium. Uptake defects attributable to necrosis are permanent and therefore preclude normal uptake of tracer or reversible ischaemic defects despite restoration of myocardial perfusion through patent grafts. In areas of necrosis, graft occlusion or graft patency may be equally likely.[6] Grafts subtending these regions must, therefore, be classified as equivocal or of indeterminate patency (Fig. 3). In addition, grafts subtending suspicious uptake defects seen in only one view were also classified as equivocal.

SCINTIGRAPHIC LOCALISATION OF GRAFTS

These criteria were used to analyse individual coronary bypass grafts whose myocardial territories of supply were identified by our knowledge of the scintigraphic anatomy of ungrafted coronary disease.[7] The regions relevant to each graft are seen in Fig. 4, and listed below.

Left anterior descending graft
Anterior view; anterior wall and apex.
Left oblique view; septum.
Left lateral view; anterolateral wall and apex.

Right coronary graft
Anterior view; posteroinferior wall.
Left oblique view; inferior wall.
Left lateral view; no contribution.

Left circumflex graft
Anterior view; no contribution.
Left oblique view; posterolateral wall.
Left lateral view; inferolateral wall.

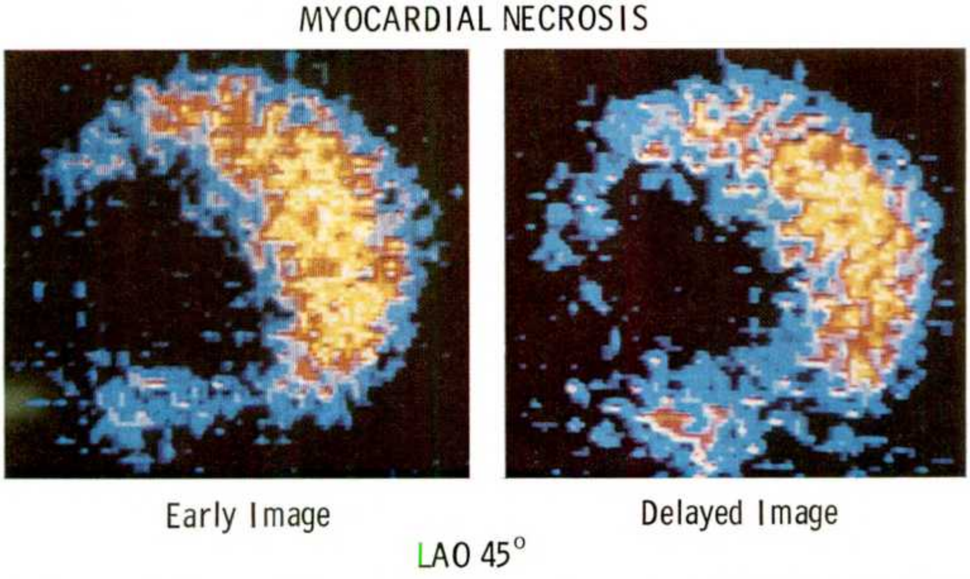


Fig. 3 *^{201}Tl myocardial scintigram LAO 45°. The severe septal tracer defect seen in the left image persists in the delayed image* (right) *indicating necrosis of the septum. In this situation patent or occluded left anterior descending grafts are not distinguishable.*

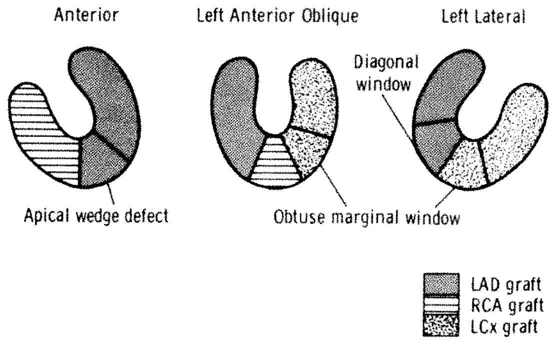


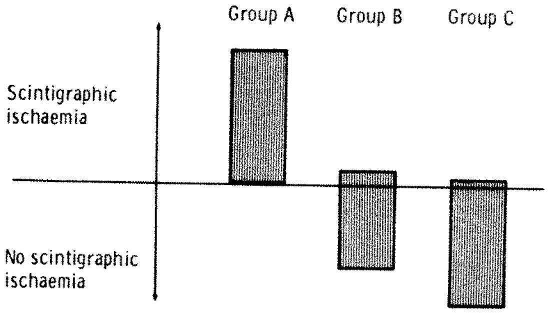
Fig. 4 *Diagrams of ^{201}Tl myocardial scintigrams in three views indicating the territories supplied by coronary grafts.*

In addition to quantification all scintigrams were reviewed independently by at least two observers without knowledge of the corresponding coronary angiograms. Observer agreement in the interpretation of scintigrams by visual and quantitative methods was excellent (>90%) but consensus of a third observer was sought when necessary.

Statistical comparison of data was performed using the χ^2 test with Yates correction or the Fisher exact test.

Results

Fig. 5 shows the relation between chest pain and regional myocardial ischaemia detected by reversible tracer defects appearing in the ^{201}Tl scintigram. All 18 patients with typical angina pectoris (group A) had at least one tracer defect in their scintigrams attributable to myocardial ischaemia. In comparison, only five of these patients had a positive stress electrocardiogram. Ischaemic defects were found in regions of the myocardium subtended by occluded grafts in 11 patients and functionally inadequate grafts in six patients (two grafts stenosed, four grafts with poor distal run-off). In one patient tracer deficit was caused by severe ungrafted coronary disease. Angiography showed 24 out of 47 (51%) grafts occluded in this group.



	Group A	Group B	Group C
No. of necrotic regions	8	4	7
Positive stress electrocardiograms	5	0	1
Grafts patent	23/47 (49%)	21/30 (70%)	35/42 (83%)

Fig. 5 *Relation between chest pain and scintigraphic evidence of myocardial ischaemia in three groups of patients. Group A had typical angina pectoris; group B had atypical angina pectoris; group C had no chest pain.*

In contrast, only two out of 13 patients with atypical chest pain (group B) had evidence of myocardial ischaemia in the ^{201}Tl scintigram ($P < 0{\cdot}0005$). Both patients had reversible uptake defects in the left anterior descending territory. Left anterior descending graft occlusion was confirmed by angiography. The remaining patients had normal tracer uptake or fixed defects of tracer attributable to myocardial necrosis. No patient had a positive stress electrocardiogram. In this group nine out of 30 (30%) grafts were occluded on angiography (group A and B, NS).

Finally, 16 out of 17 patients without chest pain (group C) had no evidence of myocardial ischaemia in the ^{201}Tl scintigram. One patient had a reversible uptake defect in a small area of the posterolateral wall corresponding to an occluded obtuse marginal graft. Presumably this was a region of painless ischaemia. Interestingly, this was the only patient without chest pain who had a positive exercise electrocardiogram. In this group the majority of grafts 35/42 (83%) were patent at angiography (group A and C, $P < 0{\cdot}005$; group B and C, NS).

Exercise electrocardiography failed to detect 15 out of 21 patients with scintigraphic evidence of regional myocardial ischaemia.

PATENT GRAFTS

Of 119 grafts, 77 (65%) were found to be patent by contrast angiography. Eleven grafts were of indeterminate patency by scintigraphy because they subtended necrotic myocardium (seven grafts) or because suspicious defects were seen in only one view (four grafts). Sixty-one grafts were correctly predicted patent from the ^{201}Tl myocardial scintigram. If the 11 equivocal grafts are excluded, the sensitivity rate of the detection of a graft patency is 61/66 (92%) (Fig. 6).

False negatives

Sixteen patent grafts were incorrectly predicted occluded from the myocardial scintigram, that is apparent false negatives for graft patency. Though patent, five grafts were functionally inadequate because of significant graft stenosis (two grafts) or poor run-off (three grafts), thus mimicking graft occlusion. In this false negative group only one patent graft had angiographically good distal run-off compared with 47 patent grafts with good distal run-off in the true positive group ($P < 0{\cdot}001$).

Eleven occluded grafts were incorrectly predicted patent by ^{201}Tl scintigraphy and thus classified as false positives for graft patency or, alternatively, as the false negatives for graft occlusion discussed below. Thus, the predictive accuracy of ^{201}Tl scintigraphy in the determination of graft patency is $61/61+11$ (85%).

OCCLUDED GRAFTS

At angiography, 42 (20 graft stumps and 22 grafts not shown) out of 119 (35%) grafts were presumed occluded. Twenty-one of these grafts were correctly predicted occluded from analysis of appropriate regions of the myocardial scintigram. Ten occluded grafts were classified equivocal by scintigraphy because they subtended necrotic areas (eight grafts) or were associated with moderate tracer reduction seen in only one view (two grafts). The latter two grafts supplied the left anterior descending artery which, in one case, showed considerable hypertrophy of its first septal branch, serving as a major collateral channel; in the other case, the native left anterior descending was only moderately diseased (60% stenosis). If these 10 occluded grafts are excluded, sensitivity rate for graft occlusion is 21/32 (66%) (Fig. 6).

False negatives

In contrast, 21 occluded grafts were predicted patent by ^{201}Tl scintigraphy because no tracer defects were seen in regions corresponding to the territory of graft supply, that is apparent false negatives for graft occlusion. It was interesting that in 11 occluded graft territories three regions were well supplied by collateral vessels, three regions were supplied by native vessels with less than 70 per cent narrowing of the coronary lumen, and one region was in the territory of a recessive right coronary artery and, therefore, very small. Only four occluded grafts incorrectly thought patent from the scintigram subtended regions supplied by severely diseased native vessels with inadequate development of coronary collateral vessels.

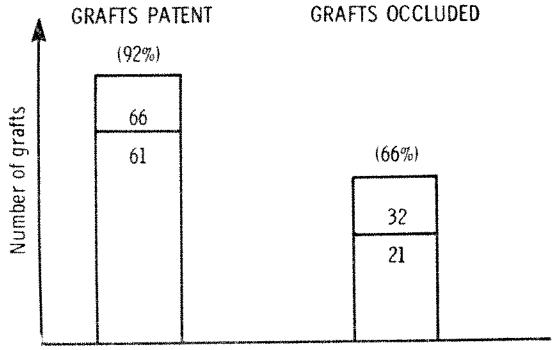


Fig. 6 *Number of grafts predicted patent and occluded by ^{201}Tl scintigraphy.*

The protective role of coronary collaterals in preventing the scintigraphic detection of graft occlusion could be extended to partial protection in four patients with graft occlusion who had well-developed collateral channels and less profound tracer defects than expected from the severity of corresponding coronary artery disease. One patient had partial scintigraphic protection in the territory of a severely diseased obtuse marginal artery left ungrafted but supplied by plentiful collaterals. However, no protection was seen in the scintigrams of two patients with severe disease of the right coronary artery and an occluded right coronary artery graft despite retrograde collateral filling from the left coronary artery. One of these patients had severe disease in all collateral donor vessels and no patent grafts.

Five patent grafts predicted occluded by scintigraphy were classified as false positives for graft occlusion and have already been discussed as the false negatives for graft patency. Though anatomically patent these grafts all had poor function. Thus, the predictive accuracy of graft occlusion determined by scintigraphy is $21/21+5$ (81%).

Mid-septal tracer transition of left anterior descending graft patency

Several patients had scintigrams showing deficit of tracer in the upper half of the septum, with preservation of normal tracer accumulation in the lower half of the septum, that is a mid-septal transition of tracer uptake as illustrated in Fig. 7. This is paradoxical, for the scintigraphic criteria of graft patency and graft occlusion are both present in the same territory of one grafted vessel, the left anterior descending artery. The majority of patients with this appearance had no other defects in the distribution of this artery when other scintigraphic projections were analysed. This septal pattern of tracer distribution was attributed to better perfusion of the lower, more distal septum in preference to the upper, more proximal septum, and was thought most likely to occur with a patent left anterior descending graft which had good distal run-off. Subsequent angiographic correlations confirmed

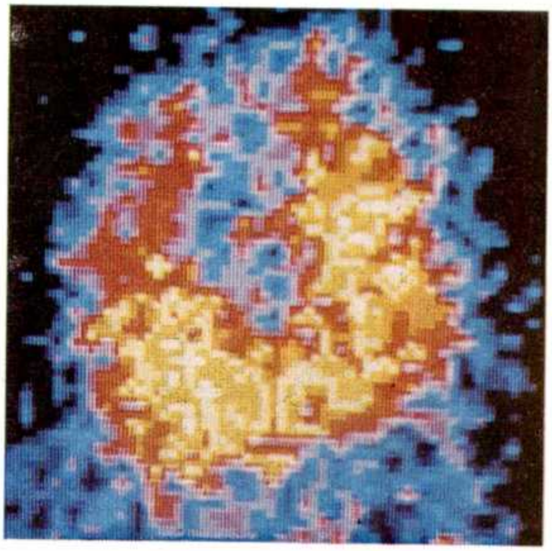


Fig. 7 *Tracer deficit in the upper septum coexists with normal tracer accumulation in the lower septum causing mid-septal transition of tracer in a patient with a patent left anterior descending graft and good distal run-off.*

that this interpretation was probably correct, since the sign of mid-septal tracer transition was most commonly seen in patients with patent left anterior descending grafts and good distal run-off (18 out of 33 (54%)). Moreover, all these patients had severe proximal left anterior descending disease, with very poor filling of the proximal segment from native coronary and graft injections of contrast medium. It was remarkable that completely normal uptake of tracer in the septum occurred in only eight patients with patent left anterior descending grafts. Fixed uptake defects extending down the whole septum resulting from myocardial necrosis were seen in seven patients with patent left anterior descending grafts and prevented the scintigraphic recognition of graft patency. Only one patient with a patent left anterior descending graft had reversible tracer reduction in the whole septum mimicking a graft occlusion. This patient had severe stenosis of the left anterior descending graft at its distal anastomosis causing complete septal ischaemia.

Mid-septal tracer transition was not a specific sign of a patent left anterior descending graft with good distal run-off, since four patients with an occluded graft also exhibited this septal distribution of tracer, though three of these patients did have evidence of left anterior descending graft occlusion in other views.

The usual sign of left anterior descending graft occlusion was a reversible tracer deficit extending down the whole septum. Five patients with an occluded left anterior descending graft had this appearance which was irreversible in one patient because of septal necrosis. Only one patient with left anterior descending graft occlusion had completely normal accumulation of tracer in the septum. These findings are summarised in Fig. 8.

APICAL WEDGE DEFECT IN ANTERIOR VIEW

Fig. 9 shows an example of abnormal tracer reduction at the cardiac apex causing a wedge-shaped defect. In our experience this defect is usually attributable to left anterior descending coronary disease and often indicates that the distal left anterior descending lumen is of poor calibre.[7] In the context of a patent left anterior descending graft the appearance of this apical defect usually meant that the graft had poor distal run-off, as shown by the following analysis.

(a) *Patent left anterior descending graft*

Four patients with a patent left anterior descending graft but necrosis in the left anterior descending territory all had fixed apical tracer deficit in the anterior view. In the absence of myocardial necrosis 21 out of 28 patients (75%) with patent left anterior descending grafts had completely normal tracer accumulation in the cardiac apex. All these patients

	Number of Grafts Patent	Number of Grafts Occluded
Normal septum	8	1
Mid-septal transition	18	4
Whole septal reduction	7	5

Fig. 8 *The relation between left anterior descending graft integrity and corresponding patterns of tracer distribution in the septum.*

had good distal run-off from their left anterior descending graft. The remaining seven patients all had abnormal apical reduction of tracer. Two of these patients had very poor graft run-off and two patients had significant stenosis of the graft at its distal anastomosis. In a further two patients the apical deficit in the anterior view was not specific for left anterior descending disease but could be attributed to left circumflex disease producing severe tracer deficit in the lower posterolateral wall of the myocardium (left circumflex territory) when seen in the left anterior oblique view. These false positive left anterior descending apical defects were easily identified when all four views of the myocardial scintigram were compared. Finally, the distal run-off from one left anterior descending graft supplied a large obtuse marginal vessel cross-filling through prominent collateral channels seen on the angiogram. In this patient dynamic exercise may have precipitated a steal phenomenon whereby graft flow was shunted away from the cardiac apex along collateral channels to the obtuse marginal territory, thus producing the relative deficit of apical tracer accumulation shown in Fig. 9.

(b) *Occluded left anterior descending graft*

Two patients with occluded left anterior descending grafts subtending myocardial necrosis had significant apical tracer reduction similar to those patients with patent left anterior descending grafts and myocardial necrosis.

Five patients with an occluded left anterior descending graft but persistence of a good calibre distal left anterior descending lumen all had completely normal tracer accumulation in the cardiac apex seen in the anterior view. Conversely, three out of four occluded left anterior descending grafts which subtended a poor calibre distal left anterior descending lumen did have significant tracer reduction in the cardiac apex.

(c) *No left anterior descending graft*

Two patients had significant proximal left anterior descending disease left ungrafted because the distal lumen of this vessel was of poor calibre. Both patients had apical defects of tracer accumulation.

In contrast, three patients with no left anterior descending disease and no left anterior descending graft, but grafts to other coronary vessels, had completely normal apical accumulation of tracer.

Thus, in summary, anterior view deficit of tracer at the cardiac apex, in the absence of myocardial necrosis, was a highly specific sign of impaired run-off from a patent left anterior descending graft but could not distinguish stenoses in the graft from poor calibre native distal vessels.

Ungrafted coronary disease detected in scintigram

Thirty-two patients had tracer defects in the myocardial scintigram attributable to severe coronary artery disease which had not received venous bypass grafts. Only three patients had ungrafted coronary disease which was not detected by scintigraphy. One patient had a 50 to 60 per cent stenosis

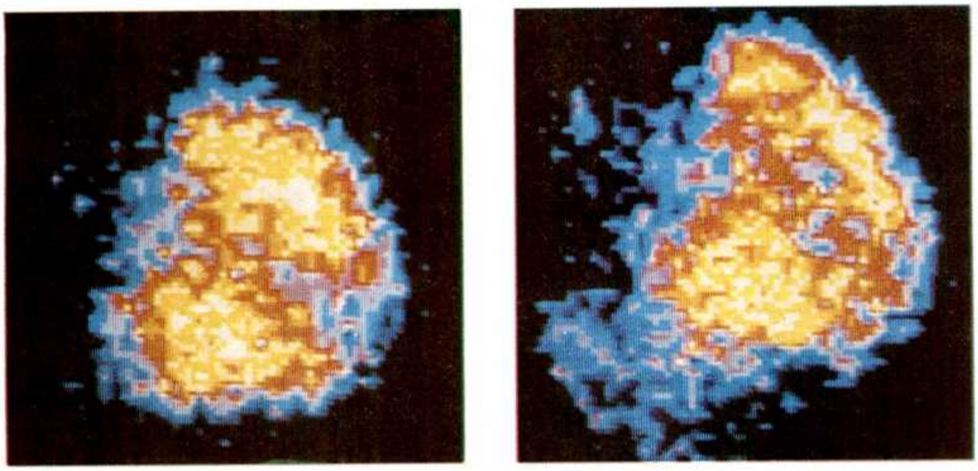


Fig. 9 *Anterior view* ^{201}Tl *myocardial scintigrams. A significant defect of tracer was seen at the cardiac apex in the early post-exercise scintigram* (left) *which disappeared in the delayed scintigram* (right) *indicating apical ischaemia on exercise. This patient had a patent left anterior descending graft filling an obtuse marginal artery through collateral vessels. A steal phenomenon at the cardiac apex may have been precipitated by exercise.*

of the left circumflex vessel and a patent left anterior descending graft; one patient had severe disease in a recessive right coronary artery subtending only a small area of myocardium, and the final patient had a 70 per cent stenosis in a trifurcation obtuse marginal artery which subtended myocardium already served by a separate patent obtuse marginal graft.

The diagonal branch of the left anterior descending was the most frequent ungrafted vessel associated with uptake defects in its territory of supply (28 patients). Independent diagonal branch left anterior descending disease was found in 12 patients with scintigraphic evidence of ischaemia and in two patients with evidence of myocardial necrosis in the distribution of this vessel.

Fourteen patients had severe coronary disease affecting the left anterior descending before its main diagonal branch. Though 11 of these patients had a patent left anterior descending graft the main diagonal branch of the left anterior descending could not be visualised, either anterogradely by left coronary arteriography, or retrogradely by selective graft angiography. The remaining three patients had occluded left anterior descending grafts with severe left anterior descending coronary disease arising before its diagonal branch. All these patients had evidence of diagonal branch ischaemia in the ^{201}Tl scintigram. Thus, in the absence of a separate graft to the main diagonal branch of the left anterior descending, scintigraphic evidence of ischaemia was found in the distribution of this vessel regardless of the status of the main left anterior descending graft.

Conversely, in 14 patients who had excellent opacification of the main diagonal left anterior descending branch the characteristic scintigraphic uptake defects (diagonal windows) caused by left anterior descending diagonal branch ischaemia were never seen.

Only three patients had angiographic evidence of diagonal branch left anterior descending disease with no corresponding 'diagonal window' in the ^{201}Tl scintigram, that is false negatives. One of these patients achieved a rather low work-load on the bicycle ergometer, and it is possible that this was insufficient to provoke a perfusion defect, for the sensitivity of exercise scintigraphy to detect critical stenoses increases with the level of exercise.[8]

Thus, after aortocoronary bypass graft surgery the scintigraphic diagonal window was a highly sensitive and specific marker of persistent ischaemia in the diagonal branch of the left anterior descending despite a patent graft to the parent vessel (sensitivity rate 28/31 (90%), specificity rate 14/14 (100%)).

Discussion

Thallium-201 (^{201}Tl) behaves as a biological analogue of potassium[9] and is more suitable for imaging with conventional scintillation cameras than other monovalent cations.[10] Its initial distribution within viable myocardium is proportional to the regional coronary blood flow prevailing at the time of intravenous administration.[4] Tracer redistribution is seen later in regions of resolving ischaemia.[11] Several recent studies have shown that exercise ^{201}Tl myocardial scintigraphy is a sensitive technique to detect and localise obstructive coronary artery disease.[7 12 13] Its value in the assessment of aortocoronary bypass graft surgery by comparing pre- and postoperative myocardial scintigrams has also been reported.[14 15] This study was designed to determine the role of postoperative exercise ^{201}Tl myocardial scintigraphy alone in the non-invasive evaluation of aortocoronary bypass graft surgery.

The rather low graft patency rate (65%) found in this series accords with the highly selected group under study; nearly two-thirds of patients were evaluated because of chest pain. Nevertheless, these patients are typical of those requiring further assessment after aortocoronary bypass graft surgery.

The quality of chest pain was a useful guide to the degree of myocardial revascularisation; all patients with typical angina pectoris had scintigraphic evidence of persistent regional myocardial ischaemia, whereas most patients who were free from pain did not have ischaemic defects in their scintigrams ($P < 0{\cdot}0005$). This was consistent with the fact that, at angiography, graft occlusion was found more frequently in patients with typical angina than in those without chest pain ($P < 0{\cdot}005$). Patients with atypical chest pain did not have a significantly different graft occlusion rate than those without chest pain, nor was there any difference in the prevalence of scintigraphically detectable ischaemia between these groups. Most patients with atypical pain after operation had similar pain before operation. In contrast, the prevalence of myocardial necrosis was not significantly different among these three groups of patients. Thus, this study supports the belief that the most important mechanism of pain relief after aortocoronary bypass graft surgery is effective myocardial revascularisation[16] rather than myocardial necrosis, placebo effects, or denervation.

Nevertheless, a high proportion of cases did have evidence of significant ischaemia after aortocoronary bypass graft surgery, particularly in the proximal branches of the left anterior descending coronary artery, despite angiographically patent grafts. Experimental work[17 18] has shown that partition of flow between graft and native vessel is determined by their relative diameters and the degree of stenosis in the proximal coronary artery. In the presence of a 50 per cent proximal coronary stenosis a graft always carried more than 90 per cent of total flow. These authors suggested that complete occlusion of a bypassed proximal coronary segment was likely in view of the poor flow carried in this portion of the vessel. Clinical studies have confirmed these predictions, for Aldridge and Trimble and others[19-21] have all reported progression of significant proximal coronary disease to total occlusion in 17 to 46 per cent of cases after bypass grafting. New occlusions occurred most commonly in grafted coronary arteries.

The pattern of midseptal tracer transition described in the scintigrams of our patients with patent left anterior descending grafts supports the concept that ischaemia in the proximal coronary segment is common and sufficiently severe to be detected scintigraphically. Midseptal transition of tracer is emphasised as a sign of a patent left anterior descending graft with good distal run-off rather than a marker of left anterior descending graft occlusion for which evidence should be obtained from other views in addition to the left anterior oblique projection.

Relative ischaemia was commonly found in the distribution of angiographically normal diagonal branches of the left anterior descending when grafts to the main segment of the distal left anterior descending were patent. In this situation we suggest that if the main diagonal branch of the left anterior descending is a large and important vessel it should receive an independent venous graft at the time of aortocoronary bypass graft even though it appears angiographically free of disease.

The predictive accuracy of postoperative ^{201}Tl myocardial scintigraphy is remarkably high using the criteria of graft integrity previously outlined. It was interesting that patent grafts could be predicted more accurately than occluded grafts which were usually not detected because tracer uptake was preserved by flow through native and collateral vessels. A similar effect of the coronary collateral circulation is seen in patients with ungrafted coronary artery disease.[22] Flow through patent grafts subtending necrotic myocardium is unlikely to make a significant contribution to pain relief, though it cannot be disputed that in some cases such patent grafts may provide important collateral channels to other regions of the myocardium. Similarly, it is doubtful whether occlusion of grafts subtending regions of myocardial necrosis can be seriously considered as a cause of recurrent angina pectoris.

Our results confirmed that the occurrence of regional necrosis was unrelated to recurrent chest pain. Equal numbers of occluded and patent grafts subtended necrotic myocardium and indicated that necrosis did not predispose to graft occlusion. In this predictive analysis exclusion of grafts subtending necrosis is justified by their functional irrelevance to the relief or recurrence of angina pectoris. Failure to predict graft integrity in regions of myocardial necrosis is, therefore, not an important limitation of ^{201}Tl myocardial scintigraphy.

On the basis of these results we suggest that patients with recurrent or persistent chest pain after aortocoronary bypass graft should be investigated initially with exercise ^{201}Tl myocardial scintigraphy and only referred for coronary and graft arteriography if there is evidence of myocardial ischaemia suggesting occluded or poorly functioning grafts, or significant ungrafted coronary disease. Moreover, presumptive knowledge of individual graft status at coronary arteriography avoids prematurely abandoning attempts to opacify grafts which are patent yet often elusive. In addition ^{201}Tl myocardial scintigraphy can be used to interpret postoperative coronary arteriograms in which graft identities are uncertain or suspected patent grafts have not been adequately demonstrated.

It is interesting that this high predictive accuracy was achieved by analysing postoperative ^{201}Tl myocardial scintigrams alone without the refinement of preoperative scintigrams for comparison. We therefore agree with Greenberg *et al.*[23] that postoperative myocardial scintigraphy alone is invaluable in documenting the results of aortocoronary bypass graft surgery non-invasively.

Repeated non-invasive evaluation of graft status is an advantage of ^{201}Tl myocardial scintigraphy not provided by coronary arteriography. Graft closure may be symptomatically silent and thus go undetected in the absence of routine graft angiography, a procedure not acceptable to all patients. Serial ^{201}Tl scintigraphy has good reproducibility[8] and may be a more attractive alternative technique to determine graft closure rates, particularly if early postoperative scintigrams and angiograms have been correlated previously.

Finally, in patients with failed aortocoronary bypass graft operations ^{201}Tl scintigraphy can indicate regions of residual myocardial ischaemia relevant for revascularisation and distinguish necrotic myocardium unlikely to benefit from further surgery.

In conclusion, postoperative exercise ^{201}Tl scintigraphy alone is a highly sensitive and specific technique in the preliminary investigation of recurrent angina pectoris after myocardial revascularisation and gives a new cutting edge to the logical planning of further surgery.

We thank Dr Lawson McDonald for referring many of the patients included in this study.

Dr R J Wainwright was supported by a British Heart Foundation grant during the completion of this work.

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Innocent murmurs and third heart sounds in Black schoolchildren*

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SUMMARY Normal auscultatory findings were studied during a heart survey in which 12 050 Black schoolchildren, aged 2 to 18 years, were examined by cardiologists. Physiological third heart sounds were detected in 96 per cent of children, innocent systolic murmurs in 72 per cent, and innocent mid-diastolic murmurs in 0·27 per cent. The term 'innocent systolic murmur' was used for vibratory systolic murmurs (70%) and pulmonary ejection systolic murmurs (4·2%) but distinct separation of these two murmurs was often difficult. Vibratory systolic murmurs were present throughout the age range. Important features in differentiating innocent systolic murmurs from those caused by mild organic heart disease included the intonation, site of maximal intensity, timing in systole, and behaviour with postural change. Innocent mid-diastolic murmurs are short murmurs occurring immediately after the third heart sound in children, with no supportive evidence of organic heart disease.

Cardiology has made considerable progress over the past half century and improvement in diagnostic and surgical techniques has led to an increased understanding of many forms of heart disease and their management. Of equal importance is the definition of the auscultatory features of the healthy heart and the recognition of normal variations. In 1909, George Still[1] gave his classical description of the vibratory systolic murmur and, nearly two decades later, Mackenzie[2] still campaigned for the widespread medical acceptance of innocent systolic murmurs. It was not possible at that time to differentiate these from abnormal murmurs except by the exclusion of other evidence of organic heart disease. Levine[3 4] introduced a classification of systolic murmurs based on intensity alone. This classification is excellent for record purposes but is of limited value in predicting the innocent or pathological nature of a systolic murmur.[5] Leatham[6] classified systolic murmurs into ejection and regurgitant types on the basis of anatomical and haemodynamic considerations and he later clarified[7] some of the auscultatory features of the normal heart. There have been subsequent contributions,[8–10] and today the clinical recognition of an innocent murmur usually presents little difficulty to the skilled auscultator.[11] This recognition is of the utmost importance[12–14] since innocent praecordial murmurs occur most frequently in children and young adults and are commonly detected when auscultation is performed as part of routine examinations at schools or during unrelated illnesses. In such instances, young patients and their parents need positive reassurance that there is no organic cardiac lesion in order to avoid incorrect management or even the development of a cardiac neurosis.[15–17]

Several studies on the incidence of innocent systolic murmurs have been reported.[8 12 18] In one series,[18] 96 per cent of healthy children between 3 and 14 years of age had a systolic murmur. In Johannesburg, a survey on 200 White schoolchildren,[12] aged 2 to 12 years, yielded a prevalence rate for innocent murmurs of 84 per cent. In May 1972, a survey[19] was undertaken on Black schoolchildren of the South Western Townships near Johannesburg (Soweto) with the primary objective of determining the incidence of rheumatic heart disease. The large number of children who had to be examined provided the opportunity of making other cardiological observations, including the incidence of non-ejection systolic clicks and as-

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*Supported by the South African Medical Research Council, Anglo-American Corporation of South Africa Ltd, South African Breweries Institute, and the Stella and Paul Loewenstein Cardiac Fund of the University of the Witwatersrand.

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Received for publication 23 July 1979

sociated mitral systolic murmurs[20] as well as congenital heart disease.[21] We now present and discuss data on the incidence of innocent murmurs and physiological third heart sounds.

Subjects and methods

A stratified random sample of 12 050 children from crèches and schools of Soweto were examined during the period of May to October 1972. A detailed account of the sampling technique and methods has been given previously[19] but relevant features will be repeated. The ages of the children ranged from 2 to 18 years (Fig. 1), and the number of boys and girls was equal.

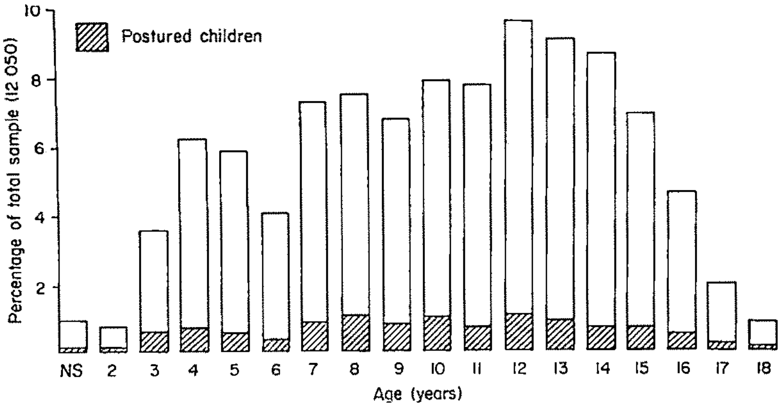

Fig. 1 *Age distribution of schoolchildren in the Soweto heart survey. The age was not stated (NS) on the forms of about 1 per cent.*

EXAMINATION

The medical team consisted of five cardiologists and five physicians who had all received at least six months' training in this cardiac unit. Three observers, at least one of whom was a senior cardiologist, were present at each session. Auscultation was performed on all children in the supine and left lateral positions. A random 10 per cent (Fig. 1) of the sample was also examined in the erect and squatting postures. Children with normal hearts were examined by one observer only, but if an abnormal murmur was suspected or detected, the children were examined independently by all three observers.[19] The finding of an 'innocent' mid-diastolic murmur had to be confirmed by at least one other observer and an electrocardiogram was also recorded. Examinations were carried out on three days a week over a five-month period. The average rate of auscultation of children with normal hearts was 25 an hour for each observer.

DIAGNOSTIC CRITERIA

Physiological third heart sounds

A third heart sound was regarded as physiological when it was heard in the absence of any abnormal cardiac findings[7, 14]. Thus third heart sounds associated with non-ejection clicks or late systolic murmurs were excluded from the analysis.

Innocent systolic murmurs

The two innocent systolic murmurs assessed were the vibratory systolic murmur[1] and the pulmonary ejection systolic murmur. Though some authors[15, 16] have suggested that the term 'innocent systolic murmur' be used for all unimportant murmurs, we excluded murmurs resulting from haemodynamically insignificant congenital anomalies such as minute ventricular septal defects[22]. Such murmurs are not completely innocuous since the lesions which give rise to them may still act as a potential nidus for infective endocarditis.[10]

The diagnostic criteria for vibratory and pulmonary ejection murmurs were those previously described.[7, 9, 23] A vibratory systolic murmur is a short crescendo-decrescendo murmur with a characteristic low-frequency musical or buzzing intonation. It is commonly of maximal intensity just inside the apex or at the left sternal border, but is frequently audible over the entire praecordium. It has a characteristic behaviour with posture, becoming softer or disappearing on standing and reappearing on squatting.[13, 24] The innocent pulmonary ejection systolic murmur is high-pitched and has a blowing quality. It is usually loudest at the second left interspace, but may also be heard over the aortic area, left sternal border, apex, and the neck, especially on the left side.[12, 13, 25] The second heart sound must be normally split and the components of normal intensity.[7, 9, 26]

'Innocent' mid-diastolic murmurs

We have applied this term to the vibrations which are heard as a short murmur immediately following a third heart sound in some apparently normal young subjects (Fig. 2) with no supportive evidence of organic heart disease.[14 27 28]

ANALYSIS

The variation in prevalence of these auscultatory findings with age, sex, and individual observer experience was assessed. A χ^2 test for homogeneity was used to assess differences. However, the large sample size necessary for the estimation of the prevalence of rheumatic heart disease rendered significance tests of little value in the analysis of common findings such as third heart sounds and vibratory systolic murmurs. In many instances, small variations in prevalence of no clinical importance were shown to be highly significant ($P < 0{\cdot}0001$). The behaviour of third heart sounds and vibratory systolic murmurs with postural change was noted.

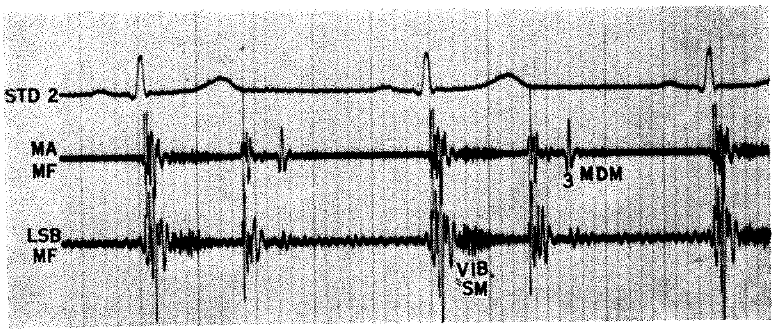

Fig. 2 *Phonocardiogram recorded on medium frequency (MF) at the mitral area (MA) and left sternal border (LSB) in an apparently normal 9-year-old child. Regular, low frequency vibrations of a vibratory systolic murmur (VIB.SM), a third heart sound (3), and a soft short mid-diastolic murmur (MDM) are shown.*

Results

Of the total of 12 050 children, 11 754 (97·5%) had normal hearts. Rheumatic heart disease[19] was diagnosed in 80 children (6·9 per 1000), mitral valve prolapse[20] in 168 (13·4 per 1000), and congenital heart disease[21] in 48 (3·9 per 1000). The overall prevalence of the auscultatory features in children with normal hearts was 96 per cent for third heart sounds, 72 per cent for innocent systolic murmurs, and 0·27 per cent for innocent mid-diastolic murmurs. In only 246 children (2·1%) was neither a third heart sound nor an innocent murmur detected.

PHYSIOLOGICAL THIRD HEART SOUNDS

A physiological third heart sound was present in 11 289 children (96·0%) and occurred with equal frequency in both sexes. Though significant variation in prevalence with age was shown ($P < 0{\cdot}0001$), the range of 93 to 98 per cent is not clinically meaningful (Fig. 3). Excluding one observer (observer D, Fig. 4), who recorded a prevalence rate of 89 per cent, there was minimal variation in the prevalence rates among the observers.

Of the third heart sounds, 26 per cent occurred as an isolated finding and 74 per cent were associated with an innocent murmur. In the routinely postured group, 1107 (94·3%) of the 1174 children had third heart sounds. All of these were present in the supine position. In 86 per cent, the third heart sound disappeared on standing but was again heard on squatting, in 9 per cent it remained in all three postures, and in 5 per cent it was present in the supine position only.

INNOCENT SYSTOLIC MURMURS

An innocent systolic murmur was present in 8475 children (72·1%) with normal hearts.

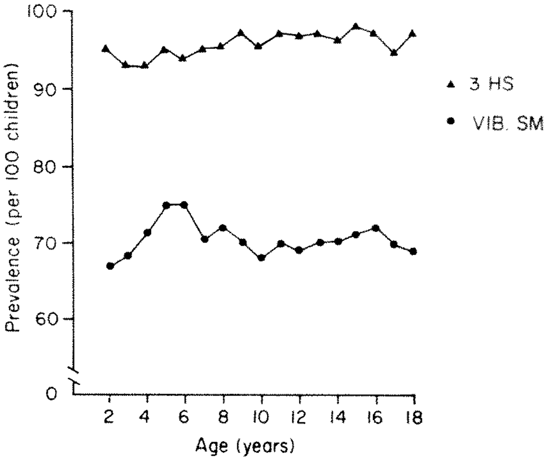

Fig. 3 *Variation in prevalence of third heart sounds (3HS) and vibratory systolic murmurs (VIB.SM) with age.*

Vibratory systolic murmurs

Vibratory systolic murmurs were detected in 70·3 per cent (8264) of children with normal hearts and were of equal prevalence in both sexes. Though the relation between prevalence and age was again statistically significant ($P < 0{\cdot}0001$), in clinical terms this was not impressive apart from a small peak in 5- to 6-year-old children (Fig. 3). There was a clinically significant variation in the prevalence among the individual auscultators (Fig. 4), and this could not be explained by differences in the ages of the children examined by them. The mean prevalence for the more experienced observers (A, B, D, F, G, and I) was 74 per cent and within this group there was minimal variation (73 to 75%), whereas the mean prevalence in children examined by the less-skilled auscultators (C, E, and H) and observer J who examined only 65 children was 66 per cent.

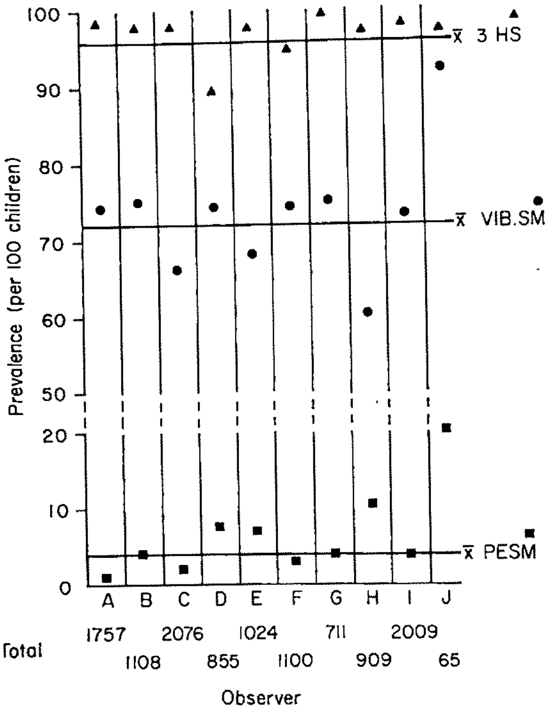

Fig. 4 *Individual observer (A–J) prevalence rates of physiological third heart sounds (3HS), vibratory systolic murmurs (VIB.SM), and pulmonary ejection systolic murmurs (PESM) in Soweto schoolchildren.*

In 99 per cent of children with vibratory systolic murmurs, a physiological third heart sound was also present. The most frequent site of maximal intensity of the murmur was the left sternal border (62%), followed by both the left sternal border and apex (17%), and the apex alone (11%). The murmur was loudest at the second left interspace in 1 per cent only and in the remainder (9%) at various combinations of these three sites.

Of the routinely postured children, 768 (65·4%) had vibratory systolic murmurs. The prevalence of these murmurs in the supine, standing, and squatting positions was 64·7, 15·9, and 57 per cent, respectively. Sixty-three per cent of the murmurs were present in the supine position, disappeared on standing, and were again heard on squatting; 24 per cent were heard in all three postures; 12 per cent in the supine position only, and 1 per cent on squatting only. In no instance was a vibratory systolic murmur detected only in the standing position. In the supine position, 95 per cent of the murmurs were of grade 2 intensity or less, 4·9 per cent were of grade 3 intensity, and 0·1 per cent (11 children) the murmur was of grade 4 intensity; 99 per cent of the murmurs still audible in the standing position were then grade 2 or less and none was grade 4. On squatting, 96 per cent were grade 2 or less and the remainder were grade 3.

Pulmonary ejection systolic murmurs

Innocent pulmonary ejection systolic murmurs were recorded in 492 of the children with normal hearts (4·2%). They were more frequent in girls with a ratio of 1·5:1 and the 15- to 18-year age group had the highest prevalence (Fig. 5). There was a significant variation in the prevalence rates among the individual observers and this was still present when the less experienced observers were excluded from the analysis ($P < 0{\cdot}001$). The mean prevalence of the more experienced group was 3·64 per cent, whereas the less experienced auscultators recorded a higher rate of 5·28 per cent.

INNOCENT MID-DIASTOLIC MURMURS

A short mid-diastolic murmur was heard in 32 (0·27%) of the children who had no other evidence of heart disease and were classified as 'normal'. Twenty-one of these children were boys. The prevalence was 0·32 per cent in 2- to 6-year-old children, 0·32 per cent in those aged 7 to 10 years, 0·16 per cent in 11 to 14-year-olds, and 0·39 per cent in the 15- to 18-year age group. The youngest child with this murmur was 3 years of age. All but three of the murmurs were detected by the more experienced auscultators. With only one exception, a vibratory systolic murmur was always an associated feature. However, none of them had an associated pulmonary ejection systolic murmur. The diastolic murmur was best heard at the apex in 25 subjects, at the left sternal border in six, and at both these sites in one. The electrocardiograms were normal in all of the children with this murmur, there were no obvious chest deformities, and the children appeared well.

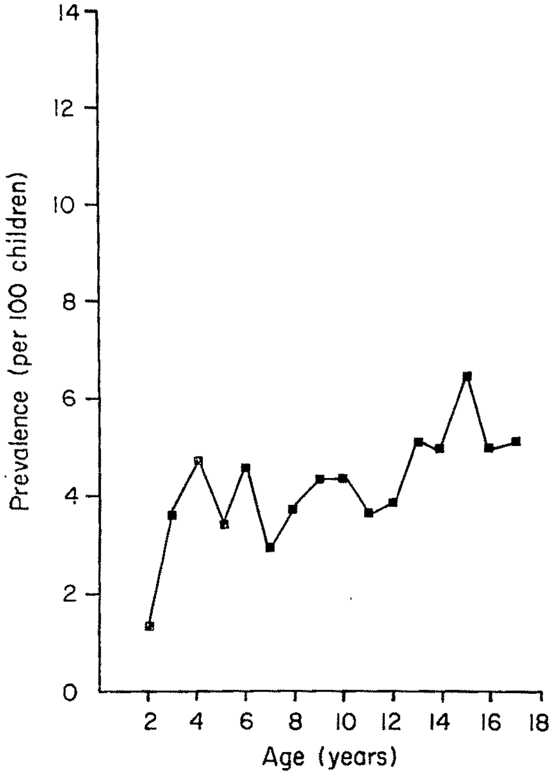

Fig. 5 *Variation in prevalence of innocent pulmonary ejection systolic murmurs with age ($P < 0{\cdot}01$).*

Discussion

Physiological third heart sounds and innocent systolic murmurs are common auscultatory findings in schoolchildren. In this survey, the vibratory systolic murmur was the most frequent of the innocent systolic murmurs. It was prevalent throughout the 2- to 18-year age group and, in contrast to the findings of other workers,[10 11 29] there was no significant fall in prevalance among adolescents. The differentiation of vibratory and pulmonary ejection systolic murmurs is often ill-defined[10 11 14] and, especially in an epidemiological study, is an academic exercise of little practical importance. In most instances, the innocent systolic murmur had the quality of both murmurs at different sites. Thus at the apex or lower left sternal border, there was the typical 'vibratory' intonation whereas at the second or third left interspace it had more of the blowing character of a pulmonary ejection murmur. This led to confusion in the interpretation of these murmurs as shown by the pronounced variation in the observers' prevalence rates. Some observers considered such murmurs to be vibratory only, whereas the interpretation of others was that both a vibratory and a pulmonary ejection murmur were present in the same child. We are aware that the classical Still's murmur, which has typical uniform low frequency vibrations on a phonocardiogram (Fig. 2), has been shown by its response to a Valsalva manoeuvre[9] and by other techniques[30] to have a left-sided origin. Nevertheless, the use of the term 'innocent systolic murmur' to include both pulmonary ejection and vibratory systolic murmurs in children is now preferred.[11]

With a background of a high prevalence of rheumatic heart disease in this community,[19] the recognition of the innocent nature of these murmurs is of special importance. Both overdiagnosis and underdiagnosis of rheumatic heart disease are harmful. Overdiagnosis may condemn some children to a prolonged antibiotic regimen, unnecessary limitation of activities, an overprotective parental attitude, difficulty in obtaining employment, and heavily loaded insurance policies.[10 31] On the other hand, underdiagnosis has the obvious danger of early rheumatic heart disease being missed and thus allowed to progress. Medical practitioners involved in the primary care of children in family practice or community health services should receive specialised training in the recognition of these murmurs. This survey suggested that even among observers training in auscultation, experience was of value in their detection. The features of most importance in differentiating innocent systolic murmurs from those caused by organic heart disease were their quality and characteristic behaviour with posture. The vibratory systolic murmur disappears or becomes softer on standing and this behaviour may partly explain why this murmur is less frequently heard in routine school examination programmes[32] in which children are auscultated in the standing position only. A vibratory systolic murmur was present in only 15·9 per cent of Soweto children in the standing position. The intensity of the murmur was not meaningful since many murmurs (63%) resulting from rheumatic mitral regurgitation were less than grade 3,[19] whereas some vibratory systolic murmurs were loud. The length and timing of the systolic murmur are also of limited value. Though a late or pansystolic murmur always indicates underlying organic heart disease,[9] a murmur in mid- or early systole may be innocent or abnormal.[5 9 18] The site of maximal intensity provides an important additional clue to the origin of the murmur particularly in small muscular ventricular septal defects,[11] but site alone cannot always be used to differentiate innocent from pathological murmurs. Though any child suspected of having an abnormal systolic murmur was examined independently by three observers and a diagnosis of organic heart disease accepted only after agreement or discussion,[20 21] we cannot exclude the possibility that a few subjects whom we have classified as normal did, in fact, have minor cardiac pathology. It is difficult, for example, on clinical examination alone, and probably impossible during an epidemiological survey, to be certain of detecting all cases of small atrial septal defect, anomalous pulmonary venous drainage, or very mild mitral regurgitation reflected by an early, sometimes intermittent, apical murmur.[5 20]

A mid-diastolic murmur, which satisfied the criteria for being innocent, was a rare auscultatory finding. This entity has not received general recognition in textbooks on cardiology. Reference has been made to a ventricular filling murmur being mimicked by a left- and right-sided third sound occurring one after the other.[14 26] We support the observations of a few workers [27 28] that short vibrations do occur in diastole in some apparently normal young individuals and may be heard as a murmur (Fig. 2). The origin of these vibrations is uncertain but they may be a result of rapid flow across the mitral or tricuspid valves. It has also been suggested[28] that the vibrations arise during distension of the left ventricular wall, since they frequently start with a loud third heart sound. We have followed other children with this murmur and it has sometimes disappeared with time despite no rheumatic fever prophylaxis. In at least one child, however, a loud non-ejection systolic click later developed which suggested that there was, in fact, a minimal abnormality of the mitral valve. Since a short mid-diastolic murmur may be the only sign of minimal organic mitral stenosis, the diagnosis of an innocent mid-diastolic murmur should only be made after a careful but non-invasive cardiac assessment to exclude this more serious alternative. In addition, children with this murmur should be followed to observe its natural history.

We thank Drs K R Bloom, D M Bramwell-Jones, E Cohen, G E Gale, K Kanarek, and J B Lakier for their assistance in the auscultation of the children, and Professor D M Hawkins and Mr B Thomas (Department of Applied Mathematics, University of the Witwatersrand), and Mr R Garrison (Epidemiology Branch, National Heart, Lung and Blood Institute, Bethesda, Maryland) for help with the statistical analyses.

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Long-term antihypertensive drug treatment and blood pressure control in three hospital hypertension clinics

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SUMMARY Prescribing patterns and blood pressure control have been studied in 1101 patients treated at three specialist hypertension clinics in Britain. Seventy-four per cent of the patients were already receiving treatment at the time they were referred by their general practitioners. Though the initial improvement in blood pressure control was satisfactory, there was often some deterioration of control over the long term. The pressure exceeded 140/90 mmHg in the majority of patients followed for a year or more. During 1971–5 diuretics remained first preference, with increasing use of beta-blockers and a distinct decline in the use of sympathetic neurone blockers both by hospital staff and referring practitioners. Multiple drug treatment was common, nearly half the patients requiring more than one antihypertensive drug. In newly treated patients the frequency of cessation of a particular class of drug because of side effects or lack of efficacy ranged from 6 per cent with diuretics to 57 per cent with adrenergic neurone blocking drugs. Long-term blood pressure control still presents many problems, and the results contrast with the more optimistic interpretations sometimes placed on short-term clinical trials of antihypertensive effect.

Clinical trials carried out in the early stages of evaluation of new antihypertensive drugs often last only a few weeks or at most a few months. Frequently the number of patients involved is small. In Britain the Committee on Safety of Medicines requires that 100 patients shall have been treated for more than a year with a new antihypertensive agent before it is marketed, but this is an unusually stringent requirement. Not surprisingly, after the introduction of compounds into day-to-day practice antihypertensive drugs are often shown in a different perspective than in clinical trials.

To investigate some of the problems of long-term antihypertensive drug treatment we have analysed blood pressure control and drug usage in 1101 patients treated for up to five years at three hypertension clinics in the United Kingdom.

Subjects and methods

Analyses were carried out on patients newly referred to and treated at hypertension clinics at Hammersmith Hospital, London, the Radcliffe Infirmary, Oxford, and King's College Hospital, London, between May 1971 and April 1975. The last patient entered in 1975 was studied until April 1976, so that the maximum period of follow-up was five years and the minimum period was one year. Clinical and laboratory data were recorded at each visit using a computer-based medical record.[1–4]

TREATMENT CATEGORIES

'Previously treated' patients were defined as those who had received antihypertensive drugs within three months before their initial visit; 'previously untreated' patients had received no such treatment.

ANTIHYPERTENSIVE DRUGS

Agents defined as antihypertensive drugs included all diuretics, beta-adrenergic receptor blocking agents, alpha-methyldopa, clonidine, reserpine, and rauwolffia alkaloids, the vasodilator hydralazine, and the adrenergic neurone blockers guanethidine, debrisoquine, and bethanidine. Analyses were carried out for specific drugs as well as for groups of compounds with similar modes of action.

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Received for publication 17 July 1979

CHOICE OF DRUGS

The first antihypertensive drug, or the first two drugs prescribed simultaneously were regarded as 'first choice' or 'first choice equal', respectively.

DRUGS STOPPED

'Cessation of a drug' was defined as stopping one drug permanently, without prescribing another in the same pharmacological group. Thus stopping a beta-blocker and starting a diuretic would be regarded as cessation of beta-blocker treatment, whereas substituting one beta-blocker for another would not.

BLOOD PRESSURES

Blood pressures were recorded by standard mercury sphygmomanometry. At the first visit to the clinic blood pressures were recorded with the patient supine after a few minutes' rest, after one minute in the sitting position, and finally after two minutes standing. At follow-up visits patients at Hammersmith Hospital had pressures recorded supine and standing, while at the Radcliffe Infirmary pressures were recorded with the patient sitting and standing. Unless otherwise stated, control was assessed for blood pressures recorded in the standing position, as these were available for all three clinics. The average of pressures over three- and six-month intervals was calculated for each patient, starting at the visit after treatment was begun (or after the first visit for 'previously treated' patients). These averages were used for group means, or for determining the numbers of patients whose systolic or diastolic pressures fell within a particular range.

Results

POPULATION STUDIED

Analyses were carried out on 499 patients at the Radcliffe Infirmary, 453 at Hammersmith Hospital, and 149 at King's College Hospital. Of these patients, 817 were already receiving treatment on referral.

BLOOD PRESSURE CONTROL

Group mean blood pressures for the first four consecutive three-monthly periods on treatment are shown in Table 1. Initial pressures and subsequent control were similar for the three clinics.

Table 1 *Blood pressure control (combined clinics)*

Previously untreated		*No.*	*Previously treated*		*No.*
Most recent untreated standing BP (mmHg)	174/111	(246)	Average standing BP (mmHg) at initial visit	170/109	(702)
3-month period 1	153/96	(284)		159/99	(782)
,, ,, 2	149/96	(170)		154/97	(464)
,, ,, 3	148/94	(158)		154/97	(398)
,, ,, 4	149/94	(130)		152/96	(313)
Latest visit	147/92	(285)		151/90	(814)

The variable numbers of patients in each period reflect the variations in duration and frequency of attendance.

Blood pressure control was further assessed by calculating the percentage of patients whose average pressures fell in different ranges. As patients were followed in the clinics for varying periods of time, this analysis was performed on cohorts followed for at least 12 months and seen at least once in the first and second three-month period and during the subsequent six months after starting treatment (Tables 2 and 3).

Blood pressures of previously treated patients were generally higher on referral (Table 3) than those of patients who had previously received no treatment (Table 2).

The main fall in pressure occurred during the first three months of treatment. Subsequently there

Table 2 *Blood pressure control in 126 previously untreated patients*

Pressure range (mmHg)	*Pretreatment* (%)	*First three months* (%)	*Second three months* (%)	*Six to 12 months* (%)
Systolic				
< 140	2	58	35	33
140–169	37	26	51	55
170–199	37	14	13	11
⩾200	25	2	1	1
Diastolic				
< 90	1	49	19	31
90–104	18	30	56	59
105–119	48	20	22	9
⩾120	33	1	2	2

Each patient was seen at least once during each period.

Table 3 *Blood pressure control in 401 previously treated patients*

Pressure range (mmHg)	*On referral* (%)	*First three months* (%)	*Second three months* (%)	*Six to 12 months* (%)
Systolic				
< 140	14	38	32	29
140–169	26	36	44	49
170–199	33	21	19	18
⩾200	27	6	5	3
Diastolic				
< 90	10	37	20	24
90–104	25	28	51	54
105–119	31	27	23	20
⩾120	34	8	6	2

Each patient was seen at least once during each period.

was deterioration in control in the third to sixth month, with little change thereafter. A similar loss of early blood pressure control was found when data for the entire population were analysed, though there were fewer regular observations on some of these patients. The latest recorded pressures of 25 previously untreated patients discharged within six months of first attendance averaged 161/100±SD 34·2/14·7 mmHg compared with 143/89±SD 20·4/16·2 mmHg in 199 patients followed for 12 months or more.

DRUG TREATMENT AND BLOOD PRESSURE CONTROL

The relation between individual drugs and blood pressure control was assessed by calculating the averages of both initial and latest blood pressures according to the drugs taken for the last three months of attendance. The mean of all pressures available (standing, sitting, lying) at a visit was used for these calculations (Tables 4 and 5). Results for systolic pressures only are shown, the pattern for diastolic pressures being similar. Blood pressures were similar for patients on beta-blockers or methyldopa, the majority of whom were also taking a diuretic. Poor pressure control was judged by levels over 170 systolic. This was seen twice as frequently in patients taking adrenergic neurone-blocking agents as with the other drugs. A similar trend for poorer control with the adrenergic neurone blockers was seen from the average of the latest pressures recorded on these drugs (Table 6).

Table 4 *Blood pressure control and drug treatment—previously untreated patients*

Drugs alone or in combination		*Diuretic*	*Methyldopa*	*Beta-blocker*	*Guanethidine/ bethanidine/ debrisoquine*
No.		198	58	97	17
Pressure range systolic (mmHg)		*Percentage in each pressure range*			
< 140	Pre-treatment	7	3	5	6
	Latest	44	48	39	41
140–169	Pre-treatment	38	26	37	35
	Latest	44	40	50	35
170–199	Pre-treatment	36	40	33	24
	Latest	12	10	10	18
⩾200	Pre-treatment	20	31	25	35
	Latest	1	2	1	6

Note: Higher proportion of patients with latest pressure over 170 mmHg systolic on guanethidine/debrisoquine or bethanidine compared with others.

CHOICE OF ANTIHYPERTENSIVE DRUGS IN PREVIOUSLY UNTREATED PATIENTS

In 284 previously untreated patients, 67 per cent received diuretics as first choice, or 'first choice equal', 20 per cent methyldopa, 18 per cent a beta-blocker, 6 per cent guanethidine, debrisoquine, or

Table 5 *Blood pressure control and drug treatment—previously treated patients*

Drugs alone or in combination		*Diuretic*	*Methyldopa*	*Beta-blocker*	*Guanethidine/ bethanidine/ debrisoquine*
No.		660	267	401	132
Pressure range systolic (mmHg)		*Percentage in each pressure range*			
< 140	On referral	15	13	14	12
	Latest	35	32	35	21
140–169	On referral	31	29	30	32
	Latest	44	45	44	39
170–199	On referral	30	35	29	32
	Latest	15	17	16	27
⩾200	On referral	25	23	26	24
	Latest	5	7	5	13

Note: Poorer blood pressure control of guanethidine/debrisoquine/bethanidine.

Table 6 *Drug treatment and blood pressure control in previously treated patients*

Drug in last three months	*Latest blood pressure (mmHg)*		*SD*	*N*
Diuretic alone	145·7/92·6	±	20/9	114
Beta-blocker plus diuretic	148·2/94	±	30/13	237
Beta-blocker alone	153·7/95·1	±	36/16	36
Methyldopa plus diuretic	150·8/93·9	±	26/13	180
Methyldopa alone	149·2/95·8	±	25/13	34
Guanethidine/bethanidine/debrisoquine plus diuretics	160·5/97·7	±	28/13	61
Guanethidine/bethanidine/debrisoquine alone	162·1/94·9	±	37/15	18

bethanidine, and 5 per cent other hypotensive agents. There was no change in the preference for diuretics between 1971 and 1975, whereas during that period the use of beta-blockers as first choice increased from 9 to 23 per cent, and that of the adrenergic neurone blockers fell from 12 to zero per cent. When first and second choice drug preferences were combined, by 1975, 45 per cent of patients received beta-blockers, 27 per cent methyldopa, and 4 per cent adrenergic neurone blockers. Ninety-five per cent of the patients treated with beta-blockers at hospital received propranolol.

The main differences between the two larger clinics were a greater preference for methyldopa at one (35% as first choice 1975), compared with the other, where beta-blockers were more often first choice (29%) and methyldopa was used initially in only 9 per cent of cases. Bendrofluazide was used as first or second choice antihypertensive (36%) at one of the clinics compared with only 1 per cent in the other, where Moduretic (29%) or Navidrex K (25%) were more often prescribed.

PRESCRIBING BY GENERAL PRACTITIONERS

Most of the drugs being taken at the time of referral of the 817 previously treated patients were prescribed by their general practitioners. Of these patients, 55 per cent were taking diuretics, 35 per cent methyldopa, 17 per cent guanethidine, bethanidine, or debrisoquine, 14 per cent beta-blockers, 3·7 per cent clonidine, and 3·3 per cent reserpine. Between 1971 and 1975 there was a fourfold increase in the use of beta-blockers, from 6·1 to 24·8 per cent of referred patients, while the use of adrenergic neurone-blocking agents fell from 22·3 to 13 per cent of patients.

CESSATION OF DRUGS IN 'PREVIOUSLY UNTREATED PATIENTS'

The proportion of patients stopping a drug and not restarting a drug from the same group was calculated for drugs given as first choice, and first choice equal or second to a diuretic. A similar analysis was carried out for diuretics given as first choice or first choice equal, with separate calculations for patients only given diuretic therapy. The chances of continuing on a drug of a particular group ranked in the order diuretic > beta-blockers > methyldopa > clonidine > sympathetic neurone-blocking agents (Table 7).

In previously treated patients this analysis was also carried out for antihypertensive drugs being taken on referral, and for drugs prescribed as first choice in the clinic (Table 7). The figures were similar to those for previously untreated patients, except for beta-blockers, which were stopped in fewer patients.

Table 7 *Patients stopping a drug permanently*

Previously untreated patients			*Previously treated patients*	
Drug	*No. in category*	*Per cent stopping*	*No. in category*	*Per cent stopping*
Beta-blocker	84	23	196	10
Methyldopa	73	29	319	36
Guanethidine/ bethanidine/ debrisoquine	23	57	155	39
Clonidine	7	43	22	45
Diuretic in combination	106	11	398	4
Diuretic alone	88	6	101	20

SINGLE AND MULTIPLE DRUG TREATMENT

The number of different antihypertensive drugs taken either on discharge or at the most recent visit was calculated for 'previously untreated' and 'previously treated' patients (Tables 8 and 9), respectively. Patients dying or lost to follow-up were excluded from the analysis. With both 'previously treated' and 'previously untreated' groups combined, there were 806 patients; and of these 54 (7% of total population) stopped treatment. Two hundred and thirty-six patients were taking one drug only,

Table 8 *Frequency of drug combinations in previously untreated patients*

Therapy at most recent clinic visit	*For patients discharged (n=84)* (%)	*For patients not discharged (n=130)* (%)	*Total (n=214)* (%)
(1) No treatment	11	1	5
(2) One drug	58	48	52
(3) Two drug combinations	29	37	34
(4) Single diuretic plus two other drugs	2	12	8
(5) Other three drug combinations	—	—	—
(6) > Three drug combinations	—	2	1

Table 9 *Frequency of drug combinations in previously treated patients*

Treatment at most recent clinic visit	*For patients discharged (n=298)* (%)	*For patients not discharged (n=294)* (%)	*Total (n=592)* (%)
(1) No treatment	12	2	7
(2) One drug	26	17	21
(3) Two drug combinations	44	48	46
(4) Single diuretic plus two other drugs	12	19	15
(5) Other three drug combinations	3	8	6
(6) > Three drug combinations	3	5	4

and of these, 65 per cent were on a diuretic, 17 per cent on a beta-blocker, 13 per cent on methyldopa, 3 per cent on clonidine, and 2 per cent on an adrenergic neurone blocker.

The majority of patients were taking two or more drugs simultaneously. The principal two-drug combinations in 308 patients all included diuretics, with either beta-blockers in 170 (55%), methyldopa in 112 (36%), or adrenergic neurone blockers in 26 (8%). Seventy-four patients were taking combinations of three drugs; these all included diuretics and a beta-blocker, with the addition of a vasodilator in 34 (46%), methyldopa in 28 (38%), or an adrenergic neurone blocker in 12 (16%).

TREATMENT OTHER THAN ANTIHYPERTENSIVE DRUGS

The numbers of patients taking drugs other than antihypertensive agents was calculated, and figures for the more commonly used substances are shown in Table 10. Both prescription and non-prescription remedies are included where these were reported.

Discussion

Three problems stand out from the analysis of this data, suboptimal control of blood pressure, multiple drug treatment, and frequent changes between classes of drug.

The reasons for poor blood pressure control in approximately 20 per cent of our patients are complex. Three-quarters were referred already taking antihypertensive treatment and in many cases the reason for referral was a poor response to the drugs. The results in this group are probably not typical of the average response of patients treated by family doctors in the community. However, even patients who had previously received no treatment showed less than ideal responses.

Table 10 *Drugs other than hypotensives taken during clinic attendance*

Drug or drug group	*No. of patients (population 1101)*	*Per cent of population*
Sedatives and tranquillisers	426	39
Potassium supplements (separate)	333	30
Potassium combined with diuretics	458	42
Analgesic and antiflammatory drugs	176	16
Antidepressants	111	10
Oral contraceptives	96	9
Digoxin	47	4
Weak vasodilators	46	4
Sympathomimetic amines	37	3
Allopurinol or uricosurics	29	3
Appetite suppressants	25	2
Clofibrate	24	2

Note: Some patients would have taken more than one of these different types of drug.

Failure to take treatment and unacceptable side effects are likely to have been important factors. Persistent hypertension deserves more attention so that strategies to deal with it can be devised.[5]

The major fall in blood pressure occurred during the first three months of treatment but other studies suggest that this may in part have been a result of regression upon the mean and habituation to the circumstances of the clinic rather than a specific pharmacological action of the drugs. Later there was some deterioration in control. Thus, among patients still attending the clinics, 60 per cent of previously untreated patients' pressures were above 140 mmHg systolic after a year on treatment, 13 per cent were over 170 mmHg systolic, and 20 per cent over 105 mmHg diastolic. Poor blood pressure control was more frequent in previously treated patients, despite more complex therapeutic regimens. However, the average referral pressure of these patients already on treatment was 170/109 mmHg, and it seems likely that their pretreatment pressures were substantially higher. The results emphasise that some patients are likely to have poor pressure control despite strenuous efforts by specialist clinics. More effective and, in particular, more tolerable regimens of treatment are still required.

Changes in treatment are often a result of fashion: however, one indication of effectiveness and tolerability is whether a drug is continued or stopped permanently. As many patients were referred because of side effects of treatment or resistance to prescribed treatment, patients who had received no previous antihypertensive therapy were analysed separately. However, the pattern was not very different in the previously untreated and the previously treated patients. When the figures in the two categories of patients (Table 7) are averaged, then overall diuretics appeared the best tolerated drugs, with only 13 per cent of patients stopping them permanently. They were closely followed by the beta-adrenergic blocking drugs, with 14 per cent stopping them permanently. Methyldopa occupied an intermediate position, with 34 per cent of patients starting on it stopping it permanently at some stage in their treatment. The drugs most often stopped permanently were the adrenergic neurone-blocking drugs in 41 per cent of patients, and clonidine in 44 per cent of patients.

The choice of drugs in the clinics was not random but there were wide differences in preference. It is interesting to note that the blood pressure control achieved was almost identical with the different drug regimens. The only exception was the sympathetic neurone-blocking drugs, whose use was associated with higher pressures whether the drugs were used alone or in combination. The use of this group of drugs in the clinic was generally reserved for resistant hypertension. During the study, there was an increasing preference shown for beta-blocking drugs by all three centres and their referring general practitioners. Some influence of the hospitals on local prescribing was suggested by the pattern in which different drugs were used. During the period of this study the policy of most doctors in the clinics was to start treatment with a diuretic and, if this proved ineffective, to add a beta-blocking agent or methyldopa. If the two-drug combination was inadequate a third would be added, usually the vasodilator hydralazine to the diuretic/beta-blocker combination, or a beta-blocker or adrenergic neurone blocker to the diuretic/methyldopa treatment. It is a measure of the difficulty of control with single agents that half the patients required more than one drug and a quarter more than two.

An interesting finding was the high proportion of patients who at some time took drugs which do not lower blood pressure but which might affect blood pressure control. Half the patients had taken sedatives, tranquillisers, or tricyclic antidepressants, and a fifth analgesics or anti-inflammatory drugs. Consumption of oestrogen containing contraceptive pills or medicines containing sympathomimetic amines was relatively common. Separate potassium supplements, of doubtful necessity in most hypertensives, were prescribed for nearly a third of patients.

Despite notable advances in the efficacy and tolerability of drugs available to treat hypertension, formidable problems remain for patients seen in hospital practice. Blood pressure control not uncommonly required two or more drugs, and changes in treatment. Blood pressures often remained in a range associated with an increased risk of cardiovascular disease. These aspects of care are important not only for patients presenting with severe hypertensive cardiovascular disease, but also for those in whom evidence for the benefits of life-long drug treatment is less substantial or unproven.

This research was begun with the aid of a grant from the Nuffield Provincial Hospitals Trust and has been continued with a research grant from The Department of Health and Social Security. We are grateful to many colleagues and assistants in the hypertension clinics of the participating hospitals who have taken part in the collection of the clinical information.

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Br Heart J 1980; **43:** 80–87

Ischaemic heart disease in young hypertensive women

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SUMMARY The association between hypertension and ischaemic heart disease was explored in a retrospective analysis of 50 severely hypertensive premenopausal women (presenting diastolic pressure ≥120 mmHg) under 45 years of age who were seen over a seven-year period. Twenty-two per cent of these patients had angina pectoris, and 38 per cent had Minnesota code 4-1 or 5-1 changes on the resting electrocardiogram. The contribution of other risk factors, including smoking habits, was assessed: 72 per cent of the patients smoked; significantly less smoking was found among two groups of age-matched women with less severe hypertension [diastolic pressures of 90 to 104 mmHg (n=50) and 105 to 119 mmHg (n=50)]. In these latter groups, only one patient had angina pectoris and none had 4-1 or 5-1 changes on the electrocardiogram.

Coronary heart disease is rare in premenopausal women under 45 years of age.[1 2] In the 20-year follow-up of the Framingham study[1] only one case of ischaemic heart disease was reported in premenopausal women under 45 years of age. Oliver,[3] over an 18-year period, collected a personal series of 145 female patients who were under 45 and who had electrocardiographic abnormalities supporting a diagnosis of coronary heart disease; 64 had angina pectoris and 81 had suffered a myocardial infarction. He identified three major risk factors—raised serum cholesterol, hypertension, and excessive cigarette smoking. Variable importance has also been attached to other possible influences, including oral contraceptives,[4] diabetes mellitus,[5] and a history among first degree relatives of ischaemic heart disease, hypertension, or diabetes mellitus.[6]

The present study explores the relation between hypertension and ischaemic heart disease in 150 young women.

Patients

All patients were premenopausal (menopause is defined as absence of the menses for at least one year[1]) and under 45 years of age at presentation. The first group of 50 patients were consecutive referrals to the MRC Blood Pressure Unit between 1972 and 1978. Recumbent diastolic blood pressures (fifth phase) as outpatients off treatment were equal to or greater than 120 mmHg on two occasions before admission, and mean values did not drop below 120 mmHg for the first three days in the ward. Thus these were examples of severe hypertension since blood pressure usually falls after admission to hospital.[7 8]

Two other groups of 50 patients, also premenopausal and age-matched to within four years of the inpatient group, were drawn from the files of the Glasgow Blood Pressure Clinic.[8] In 50 women diastolic blood pressures measured under the same outpatient conditions as above were in the range 105 to 119 mmHg and in 50 diastolic pressures ranged from 90 to 104 mmHg.

AETIOLOGY OF HYPERTENSION

In the group of severely hypertensive women (diastolic blood pressure ⩾120 mmHg) a possible cause for the hypertension was identifiable in 39 of the 50 patients (78%). Renal artery stenosis or occlusion was the commonest cause (23 instances). Eleven of these 23 women had arteriographic evidence of fibromuscular hyperplasia of at least one major renal artery, but no fibromuscular changes were seen in other major arteries from the level of the coeliac axis distally. Atheroma was the appearent cause of the renal artery stenosis in the other 12 patients. Five patients had, on intravenous urography, irregularly scarred kidneys suggesting chronic pyelonephritis. Four patients had chronic renal failure (serum creatinine consistently greater than 250 μmol/l). Three other patients had an aldosterone-secreting adenoma, three had a phaeochromocytoma, and one suffered from systemic lupus erythematosus. Eleven of the 50 patients in

Received for publication 2 August 1979

this group were in the malignant phase of hypertension at the time of admission (bilateral fundal haemorrhages, exudates, and papilloedema).

By contrast in the 50 patients with diastolic pressures of 105 to 119 mmHg only nine patients had possible secondary hypertension (five had radiological appearances of chronic pyelonephritis, and four were taking a combined oestrogen-progesterone oral contraceptive pill with 50 μg ethinyloestradiol.[10]) In the group with diastolic pressures of 90 to 104 mmHg seven patients had a possible cause (two with radiological evidence of chronic pyelonephritis, five taking an oral contraceptive). No patient in the two groups with milder hypertension had retinal haemorrhages, exudates, or papilloedema.

Methods

CLINICAL DATA

All data were collected retrospectively from case records. Histories were scrutinised for details of chest pain and all mentioned its presence or absence. Attention was focused on details of its character, situation, radiation, duration, frequency, relation to physical exercise, and response to drugs, though information on all of these aspects was not always recorded (see Table 1). Before presentation two patients had a history consistent with a myocardial infarction: in both, changes in the serum levels of cardiac enzymes and in the electrocardiogram (Minnesota code 1-1 or 1-2[11]) confirmed the clinical diagnosis.

Further data abstracted from all records included: past medical history—history of ischaemic heart disease or of hypertension in first degree relatives; drug history including oral contraceptives; smoking habits—people who had abstained from smoking for at least six months were classified as nonsmokers; details of the underlying disease process where investigation had revealed a cause of the hypertension; subsequent medical or surgical treatment and its efficacy; mortality between presentation and February 1979; details of coronary angiography (one patient only, with triple vessel disease). No patient had cardiac surgery.

ANGINA PECTORIS

We have employed the strict criteria for angina pectoris as laid down by Rose.[12] Angina pectoris was defined by him as 'a chest pain or discomfort with these characteristics:

(1) The site must include either the sternum (any level) or the left arm and left anterior chest (defined as the anterior chest wall between the levels of clavicle and lower end of sternum).

(2) It must be provoked by either hurrying or walking uphill (or by walking on the level, for those who never attempt more).

(3) When it occurs on walking, it must make the subject either stop or slacken pace, unless glyceryl trinitrate is taken.

(4) It must disappear on a majority of occasions in 10 minutes or less from the time when the subject stands still.'

It must be emphasised that the above definition is a rigid one and excludes several well-known variants of otherwise unequivocal angina. However, there were no patients with less typical angina in the present study.

Eleven patients have thus been classified as having angina pectoris: all satisfy the first two of Rose's criteria,[12] and nine satisfy the fourth. Data about the third criterion were not routinely recorded in this retrospective analysis, but the features listed in Table 1 are considered to justify the diagnosis of angina pectoris.

ELECTROCARDIOGRAMS

Resting electrocardiograms of all patients at

Table 1 *Characteristics of chest pain in 11 women with angina pectoris*

Case no.	*Site*	*Radiation*	*Character*	*Duration*	*Related to increased cardiac work*	*Relieved by*
1	Praecordium	No	Tight	10 min	Exercise	GTN
2	Arms	Jaw	Severe heavy	10 min	Mild exercise	GTN
3	Left side of chest	Left arm	Cramplike	NS	Exercise	Rest
4	Retrosternal	No	Heavy	5 min	Exercise	GTN
5	Central chest	Right arm	Crushing	20 min	Exercise, emotion	GTN
6	Chest	No	Tightness	10 min	Exercise	Rest
7	Retrosternal	NS	Heaviness	10 min	Exercise	NS
8	Chest	Left arm	Tightness	10 min	Walking	Rest
9	Retrosternal	No	Tightness	5–10 min	Exercise	GTN
10	Retrosternal	Left arm	Heaviness	10 min	Exercise	GTN, rest
11*	Chest	Left arm	Choking	5–10 min	Exercise	GTN, rest

* Case 11 had no electrocardiographic abnormalities of ischaemia. NS, not stated in case records. GTN, glyceryl trinitrate.

presentation were re-examined and classified according to the Minnesota code.[13] Abnormalities classifiable as 4-1 (ST depression $\geqslant 1$ mm) or 5-1 (T wave inversion $\geqslant 5$ mm), the criteria adopted by Oliver,[3] were taken as indices of myocardial ischaemia in this study. It is recognised, however (see Discussion), that false-positive and false-negative findings may result from this classification. Considerable difficulties also surround the interpretation of ST and T wave changes in exercise electrocardiograms[14 15]; these tests had not been routinely performed in patients and are not considered further.

OTHER INVESTIGATIONS

An analysis was made of the following investigations which were carried out on all patients at presentation: haemoglobin, serum electrolytes, urea and creatinine, fasting cholesterol (inpatients only). Thyroid function tests when available were also noted. Peripheral venous plasma renin and angiotensin II concentrations were measured on the majority of inpatients. Samples were collected between 8.30 and 9.30 a.m. after overnight recumbency and fasting in untreated patients who were taking either a fixed diet containing known and normal quantities of sodium and potassium, or a normal ward diet. Plasma total renin concentration was measured according to the method of Brown *et al.*[16] (20 patients) or active renin concentration according to the method of Millar *et al.*[17] (24 patients). Plasma angiotensin II concentrations were measured according to the method of Düsterdieck and McElwee.[18]

Results

(1) PATIENTS WITH DIASTOLIC BLOOD PRESSURE $\geqslant 120$ mmHg

On the basis of their clinical histories (Table 1) and electrocardiographic appearances (Table 2) the 50 severely hypertensive women have been divided into four groups. Ten patients (20%) had angina pectoris and electrocardiographic abnormalities of ischaemia (AP+, ECG+); one patient had classical angina but no ischaemia on electrocardiographic evidence (AP+, ECG−); nine patients (18%) had ischaemia on the electrocardiogram in the absence of angina pectoris (AP−, ECG+). Thirty patients (60%) were both asymptomatic and without electrocardiographic abnormalities of ischaemia (AP−, ECG−). Thus, overall, 40 per cent of these severely hypertensive women had either angina pectoris or ischaemic changes on their resting electrocardiograms or both. Mean diastolic pressures were similar in the four groups (138, 130, 139, and 134 mmHg, respectively).

Electrocardiographic abnormalities (at rest) (Table 2)
ST depression of $\geqslant 1$ mm (code 4-1) was present in all patients considered to have electrocardiographic ischaemia. T wave inversion of $\geqslant 5$ mm (code 5-1) was also present in one-quarter of these patients. Ninety-one per cent of patients with angina pectoris had ischaemic changes; 53 per cent of patients with ischaemia on the electrocardiogram had angina pectoris.

Less pronounced T wave abnormalities (code 5-2 or 5-3) were commonly present (Table 2). Had the criteria for electrocardiographic ischaemia included 5-2 changes,[19–21] five more patients would have fallen into the asymptomatic group with ischaemic electrocardiograms (Table 2). On this basis, 50 per cent of the severely hypertensive women would then have had either ischaemic electrocardiograms or symptoms of angina pectoris.

Taking an R wave of >26 mm in the lateral chest leads (code 3-1) as an index of left ventricular hypertrophy, more women with ischaemic changes had left ventricular hypertrophy than those without ischaemic changes ($\chi^2=11{\cdot}76$; $P<0{\cdot}001$). Overall, 24 patients (48%) had 3-1 changes present.

Fifteen patients (30%) had no electrocardiographic abnormality according to the code.[11]

Risk factors (Table 3)
(i) *Smoking:* Ten out of 11 symptomatic patients (91%) smoked cigarettes and 15 out of 19 patients with electrocardiographic ischaemia (79%) smoked, compared with 20 out of 30 asymptomatic patients with normal electrocardiograms (67%). The difference between symptomatic and asymptomatic patients did not reach significance ($\chi^2=2{\cdot}69$; $P>0{\cdot}05$) nor did that between patients with ischaemic and non-ischaemic electrocardiograms

Table 2 *Electrocardiogram abnormalities in 50 women with diastolic blood pressure $\geqslant 120$ mmHg*

Code	*Meaning*	*AP+ ECG+ n=10*	*AP+ ECG− n=1*	*AP− ECG+ n=9*	*AP− ECG− n=30*	*All groups n=50*
1-0	No abnormality reported	0	0	0	15	15
1-1 or 2	Q waves	2	0	0	0	2
3-1	Left ventricular hypertrophy	8	1	7	8	24
4-1	ST depression $\geqslant 1$ mm	10	0	9	0	19
4-2 or 3	Lesser ST changes	0	0	0	4	4
5-1	T inversion $\geqslant 5$ mm	2	0	3	0	5
5-2	T inversion 1–5 mm	6	0	5	5	16
5-3	T flat or diphasic	1	0	1	7	9

Table 3 *Risk factors*

Classification of patients	*No. of patients*	*Cigarette smoking*			*Serum cholesterol*			*Oral contraceptives*			*Family history*
		Non- or ex-	*<20/day*	*≥20/day*	*Normal*	*High*	*Not measured*	*Present use (within 6 mth)*	*Use in past*	*No use admitted*	*Of IHD or hypertension*
AP+ ECG+	10	1	5	4	9	0	1	1	3	6	5
AP+ ECG−	1	0	1	0	1	0	0	0	0	1	1
AP− ECG+	9	3	2	4	5	2	2	3	0	6	6
AP− ECG−	30	10	12	8	24	5	1	11	4	15	12
All patients	50	14	20	16	39	7	4	15	7	28	24

$(\chi^2=0{\cdot}73;\ P>0{\cdot}05)$. Forty-two per cent of patients with ischaemic changes smoked heavily (≥20 cigarettes per day) but so did 26 per cent of patients with non-ischaemic electrocardiograms and the difference was not significant $(\chi^2=1{\cdot}44,\ P>0{\cdot}05)$.

(ii) *Cholesterol, oral contraceptives, family history:* Data regarding these factors show abnormalities no more frequently in the symptomatic or electrocardiographically abnormal groups than among those who were asymptomatic or had normal electrocardiograms (Table 3).

(iii) *Renin and angiotensin II* (Table 4): 88 per cent of patients had peripheral venous plasma renin concentration measured when untreated, shortly after admission, and 86 per cent also had measurements of peripheral plasma angiotensin II levels. No statistical difference between symptomatic/asymptomatic or ischaemic/non-ischaemic groups was found. When renin and angiotensin II levels at presentation were related to subsequent morbid events, one patient who subsequently suffered a myocardial infarction had high peripheral plasma renin and angiotensin II levels but two others suffering a myocardial infarction and four suffering strokes had values within the normal range.

(iv) *Fibromuscular hyperplasia:* Fibromuscular hyperplasia of the coronary arteries was unlikely since changes in the renal arteries were not found more frequently among those with angina pectoris or electrocardiographic abnormalities than among those who were asymptomatic and had normal electrocardiograms (21% compared with 23%).

(v) *Malignant-phase hypertension:* Malignant-phase hypertension was present in 11 patients. Two patients had angina pectoris and ischaemic electrocardiograms; three had abnormal electrocardiograms but were asymptomatic; six did not have angina pectoris or electrocardiographic abnormalities of ischaemia. There was thus no excess of symptomatic patients among those admitted with malignant-phase hypertension.

(vi) *Others:* There were no differences in obesity, parity, or haemoglobin levels between the four groups. No patient was clinically hypothyroid, but this was only checked and confirmed biochemically in nine. Three patients had glycosuria on routine testing at presentation: in two a subsequent oral glucose tolerance test was normal, as were repeated urine estimations, and in the third renal glycosuria was shown. Thus no patient had diabetes mellitus.

(vii) *Multiple risk factors:* At least one risk factor (smoking, hypercholesterolaemia, family history, oral contraceptives) in addition to high blood pressure was present in 94 per cent of patients. Additional factors were equally common among symptomatic and asymptomatic patients.

Table 4a and b *50 women with diastolic blood pressure ≥120 mmHg: renin and angiotensin II*

Table a	*Peripheral plasma renin concentrations*				
	AP+ ECG+ n=10	*AP+ ECG− n=1*	*AP− ECG+ n=9*	*AP− ECG− n=30*	*All groups n=50*
Low renin	1	0	1	4	6
Normal renin	5	1	4	20	30
High renin	3	0	1	4	8
No result available	1	0	3	2	6

Table b	*Peripheral plasma angiotensin II concentrations*				
Angiotensin II values (pg/ml)	*AP+ ECG+ n=10*	*AP+ ECG− n=1*	*AP− ECG+ n=9*	*AP− ECG− n=30*	*All groups n=50*
<10	0	0	0	2	2
10–19	2	0	2	8	12
20–29	2	1	1	8	12
30–39	1	0	0	5	6
40–49	2	0	1	0	3
>50	2	0	2	4	8
No result available	1	0	3	3	7

Twenty of the renin samples were measured according to the method of Brown *et al.*[16], 24 samples according to the method of Millar *et al.*[17]. Results have been classified as low, normal, or high in relation to the respective normal ranges of these methods. Angiotensin II levels were estimated according to the method of Düsterdieck and McElwee[18] (normal range 5 to 35 pg/ml).

Treatment

Symptomatic improvement occurred after beta-blockade in seven of the 11 women with angina pectoris, but the possible direct antianginal effect of the beta-blockers could not be separated from the possible antianginal effect of blood pressure reduction by beta-blockers and other drugs. In six out of seven patients with symptomatic improvement the diastolic blood pressure was reduced by treatment to below 100 mmHg. The four remaining symptomatic patients continued to experience attacks of chest pain with the same frequency and one suffered a myocardial infarction; blood pressure control was poor in three of these patients with diastolic values ≥110 mmHg despite treatment.

Morbidity and mortality

Patients were followed up for from six months to six years after presentation. Morbidity (three patients with myocardial infarction, two with strokes, and three with intermittent claudication) was much commoner in patients who were symptomatic or had electrocardiographic signs of ischaemia —92 patient-years follow-up—than in patients who had initially normal electrocardiograms and were asymptomatic (two patients suffered a stroke)—122 patient-years follow-up. Mortality was also commoner but not significantly so in patients with symptoms or with positive electrocardiograms (three died—15% mortality) than in the asymptomatic group with normal electrocardiograms (one died—3% mortality). The fatal events were stroke (two) and myocardial infarction in the former group, and fungal peritonitis after peritoneal dialysis in the latter.

(2) PATIENTS WTIH DIASTOLIC BLOOD PRESSURE <120 mmHg

Table 5 shows the increase in angina pectoris and electrocardiographic abnormalities of ischaemia in relation to the height of the mean diastolic blood pressure at presentation. Minor ST and T wave changes were present in four patients with diastolic pressures in the range 105 to 119 mmHg and in one patient in the range 90 to 104 mmHg, but no patient in either group had the 4-1 or 5-1 changes which we have taken as indicative of ischaemia.

One patient only in the 105 to 119 mmHg group had a history of angina pectoris, and satisfied all four of Rose's criteria.[12] No fatality occurred during the follow-up period (410 patient-years follow-up) in the 100 patients with a diastolic pressure less than 120 mmHg. One patient, however, developed intermittent claudication and another had transient cerebral ischaemia during follow-up; both were in the 105 to 119 mmHg group.

Of the risk factors (smoking, family history, oral contraceptive usage) which it was possible to analyse in the 100 less severely hypertensive women, only smoking habits varied, and appeared to be related to the height of the diastolic pressure at presentation (Fig.). It was thus not possible to dissociate the adverse effects of smoking and hypertension. Seventy-two per cent of those with diastolic readings of ≥120 mmHg smoked compared

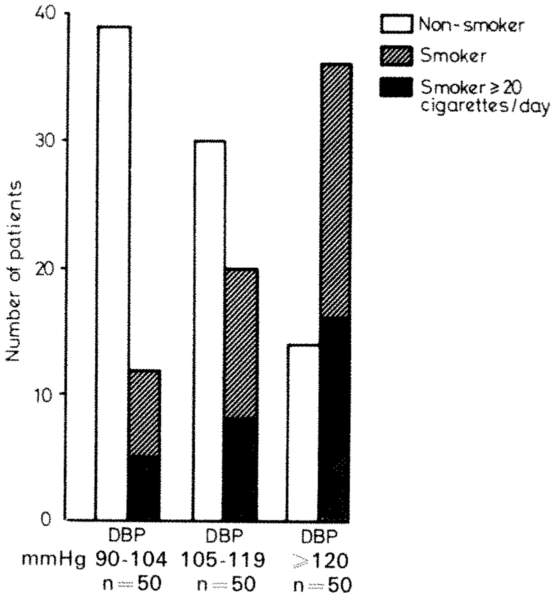

Fig. *Smoking habits in 150 premenopausal women with varying diastolic blood pressure at presentation.*

Table 5 *Angina pectoris and electrocardiographic abnormalities in 150 women with varying diastolic blood pressures at presentation*

Diastolic blood pressure (mmHg)	*Mean diastolic blood pressure (±1 SD)*	*No. of patients*	*History of angina pectoris*	*ECG ischaemia (Code 4-1; 5-1)*
90–104	96 ± 3·5	50	0	0
105–119	109 ± 4·7	50	1	0
≥120	137 ± 16·6	50	11	19

with 40 per cent of the 105 to 119 mmHg group and 24 per cent of the 90 to 104 mmHg group. Comparable percentages of heavy smokers (⩾20 cigarettes per day) were 32, 16, and 10, respectively. When smoking habits among the 50 severely hypertensive women were compared with those among the 100 women with diastolic pressures <120 mmHg the difference was highly significant ($\chi^2=21{\cdot}52$, $P<0{\cdot}001$).

Since malignant phase hypertension is known to be associated with excess smoking,[22 23] patients presenting in this way and matched patients with diastolic pressures <120 mmHg were removed from the analysis. Smoking was still significantly commoner in patients with diastolic pressures ⩾120 mmHg than in those <120 mmHg ($\chi^2=18{\cdot}93$, $P<0{\cdot}001$).

Discussion

The most notable inference which may be drawn from this study is that ischaemic heart disease, which is very rare among young women generally,[24] is common, with an incidence of one in five for angina pectoris and two in five for electrocardiographic abnormalities,[3] in a highly selected population of severely hypertensive young women.

Differing criteria in the Minnesota coded resting electrocardiogram have been applied to myocardial ischaemia in various studies. Epstein *et al.*,[19] Welborn *et al.*,[20] Bengtsson[21] and others accepted 4-1; 5-1; 5-2–6-1 or 7-1 changes as indicative of a 'coronary electrocardiogram',[21] where 5-2 represents T wave inversion of 1 to 5 mm, 6-1 represents complete atrioventricular block, and 7-1 left bundle-branch block. Oliver,[3] on the other hand, chose stricter criteria for ischaemia, namely, 4-1 or 5-1 changes, which we have adopted. Had we extended our electrocardiographic criteria of ischaemia to include 5-2 changes, 48 per cent of the women with diastolic pressures of ⩾120 mmHg would have been so affected.

Bengtsson[21] has raised the question whether 'coronary electrocardiograms' or left ventricular 'strain'[25] truly mirror ischaemia, having discovered that 29 of 1462 women in his population study had a history of angina pectoris and 23 had ischaemic electrocardiograms, but that only three had both angina pectoris and an ischaemic electrocardiogram. Our results cannot confirm this trend. Of 11 women with angina pectoris, 10 had ischaemic electrocardiographic changes, ST depression of ⩾1 mm being the most consistent abnormality. Also, 10 out of 19 women with ischaemic changes had angina pectoris, and two of the women with electrocardiographic changes only later went on to have myocardial infarctions. While significantly more women with myocardial ischaemia had left ventricular hypertrophy, this does not necessarily imply that ST depression is an effect of hypertension on the myocardium independent of ischaemia but suggests that hypertension probably predisposes to the development of ischaemia.

There are difficulties in the identification and classification of myocardial ischaemia. ST and T wave changes need not be associated with demonstrable abnormalities on coronary arteriography either in the presence of angina pectoris[26 27] or in asymptomatic patients.[28] Even myocardial ischaemia, identified by isotopic scanning[29] or by lactate extraction[30] may occur in the absence of arteriographic narrowing of the main coronary arteries. On the other hand, patients with 'typical prolonged myocardial ischaemic pain'[31] may not have 4-1 or 5-1 changes on their resting electrocardiograms.[32]

Selective referral of patients in the group with diastolic blood pressures ⩾120 mmHg might have biased results in favour of a high incidence of ischaemic heart disease. Twelve patients (24%) in this group had atheromatous stenoses of their renal arteries, and excess deposition of atheroma at other arterial sites would not be unexpected. However, only two symptomatic patients and two asymptomatic patients with ischaemia on the electrocardiogram could be accounted for in this way.

Multiple risk factors in young women with ischaemic heart disease have been found in many studies, including the present one.[2 4 6] However, by selecting premenopausal women for this study one risk factor has been removed. In the present study only the prevalence of cigarette smoking was observed to change throughout the groups with different diastolic pressures at presentation. This may in part reflect the number of patients with malignant-phase hypertension and/or renal artery stenosis in the group with diastolic pressures ⩾120 mmHg, since cigarette smoking, which has been associated with excess atheroma formation in men,[33] has also been shown to be a feature of both malignant phase hypertension[22 23] and renal artery stenosis.[34] However, Sammel *et al.*[35] have observed excess smoking (73% smokers) in a series of young women with coronary artery disease who were compared with healthy controls (21% smokers)—only 18 per cent of coronary patients in their series had diastolic blood pressures of >94 mmHg. Thus smoking has been independently associated with angina pectoris, malignant phase hypertension, and renal artery stenosis, and in this study it is difficult to separate the different associations.

Other common factors in the aetiology of the patients' hypertension and ischaemic heart disease have not been forthcoming in the present study. Fibromuscular hyperplasia of the coronary artery was one possibility considered, but fibromuscular changes of the renal arteries were no commoner in symptomatic or ischaemic patients than in asymptomatic patients. Renin and angiotensin II have been claimed as being implicated in the development of morbid or fatal events in hypertension.[36] The present study confirms Brunner's later evidence[37] that this association does not hold for ischaemic heart disease.

The effects of sustained hypertension on the myocardium may thus manifest themselves as angina pectoris or as electrocardiographic changes of ischaemia, and the severity of the rise in blood pressure allows definition of a group of premenopausal women at particularly high risk of developing ischaemic heart disease.

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Br Heart J 1980; **43**: 88–91

Beneficial effects of intravenous glyceryl trinitrate in a case of Prinzmetal angina

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SUMMARY A case is described of the successful use of intravenous glyceryl trinitrate in controlling ischaemia-induced high-grade ventricular ectopic activity occurring in a patient during a Prinzmetal angina attack. The intravenous form of glyceryl trinitrate is probably more effective than the sublingual form in controlling arrhythmias arising during acute ischaemic episodes because of prompt delivery of the drug to the coronary circulation where vasodilatation occurs. In addition, the ability to control the quantity and rate of drug delivery with an intravenous infusion offers distinct advantages in cases of coronary spasm occurring during situations such as coronary arteriography where it can be administered with careful electrocardiographic and haemodynamic monitoring.

In 1959, Prinzmetal described the clinical syndrome of variant angina pectoris characterised by distinct ST segment elevations on the electrocardiogram and a high incidence of ventricular arrhythmias (Prinzmetal *et al.*, 1959). Coronary artery spasm has been documented in these patients and is presumed to be the cause of such attacks in a substantial percentage of patients (Oliva *et al.*, 1973). The performance of coronary arteriography on patients with coronary spasm may be associated with a higher than normal risk of ventricular arrhythmias including ventricular fibrillation (MacAlpin, 1976; Yasue *et al.*, 1974). We report here the successful use of intravenous glyceryl trinitrate during arteriography for the treatment of severe myocardial ischaemia and ventricular ectopic activity in a patient with Prinzmetal angina.

Case report

The patient is a 51-year-old white man, previously in excellent health, who developed severe retrosternal chest pressure while chopping wood. He was admitted to the coronary care unit of a local community hospital where he was asymptomatic for 72 hours; serum cardiac enzyme levels were normal, and electrocardiograms were interpreted as within normal limits (Fig. 1a). He subsequently developed spontaneous recurrent bouts of severe retrosternal chest pain associated with pronounced (22 mm) ST segment elevation in leads V1–5 of the electrocardiogram (Fig. 1b). Each episode of pain and electrocardiographic abnormality was relieved within several minutes by sublingual glyceryl trinitrate, though the pain recurred in 5- to 6-hour cycles. With most episodes of chest pain, ventricular tachycardia developed at a rate of 150 beats a minute. This arrhythmia was characterised by slightly irregular runs of wide bizarre QRS complexes occurring in groups of 8 to 10 beats in a row and lasting 2 to 3 minutes. Treatment was begun with oral propranolol, 120 mg, every 6 hours; isosorbide dinitrate, 2·5 mg, sublingual, every 3 hours; and glyceryl trinitrate paste, 2·5 cm, every 4 hours. In addition, a lignocaine infusion at 1 mg/min was begun.

The patient was transferred to the Peter Bent Brigham Hospital for further evaluation. On admission, his physical examination was unremarkable except for an apical fourth heart sound. Serial electrocardiograms obtained during a pain-free interval were unchanged compared with that shown in Fig. 1a.

The day after admission, the patient underwent cardiac catheterisation. Before selective coronary arteriography could be performed, he complained of chest pain and an electrocardiographic monitor (lead II) showed distinct ST segment depression and ventricular ectopic activity (Fig. 2). Sublingual glyceryl trinitrate, 0·3 mg, was administered and, because of worsening ventricular ectopic activity, lignocaine, 100 mg, was given as an intravenous

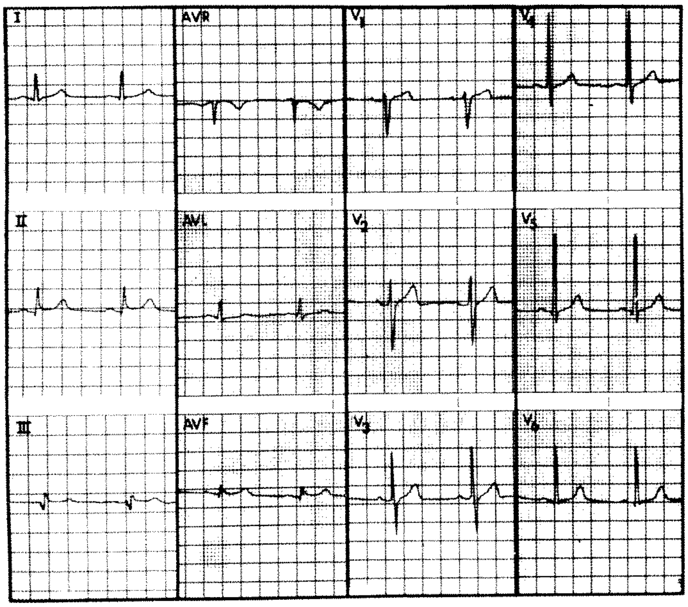

Fig. 1a *Electrocardiogram during a pain-free interval (1 mV = 10 mm).*

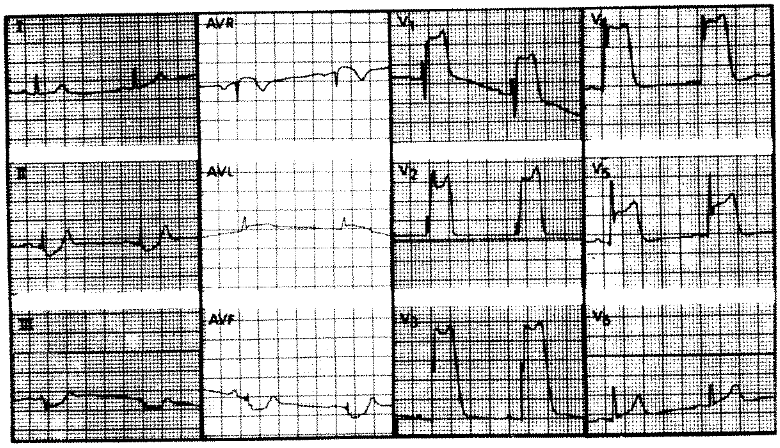

Fig. 1b *Electrocardiogram during chest pain showing distinct ST elevation in anterior praecordial leads (1 mV = 10 mm).*

bolus. The monitor rhythm strip showed an initial return of ST segments to baseline with abolition of ventricular ectopic activity. However, ST segment shift recurred, accompanied by high-grade ventricular ectopic activity including runs of ventricular tachycardia. In order to obtain prompt relief of the ischaemia-induced arrhythmias, 100 μg glyceryl trinitrate was administered intravenously as a bolus.

Fig. 3 shows the time course of reversal of the electrocardiographic abnormalities. Within 60 seconds, the ST segments had returned toward baseline and ventricular ectopic activity had disappeared. Within 120 seconds after the administration of intravenous glyceryl trinitrate, the QRS-T configuration had become normal.

Coronary arteriograms were then performed during a continuous intravenous infusion of glyceryl trinitrate at 5 to 10 μg/min and showed isolated stenosis, greater than 90 per cent, of the proximal left anterior descending coronary artery. Left ventriculography showed minimal anterior wall hypokinesis. A saphenous vein aortocoronary artery bypass graft to the left anterior descending coronary artery was performed immediately after cardiac catheterisation, and the patient subsequently had

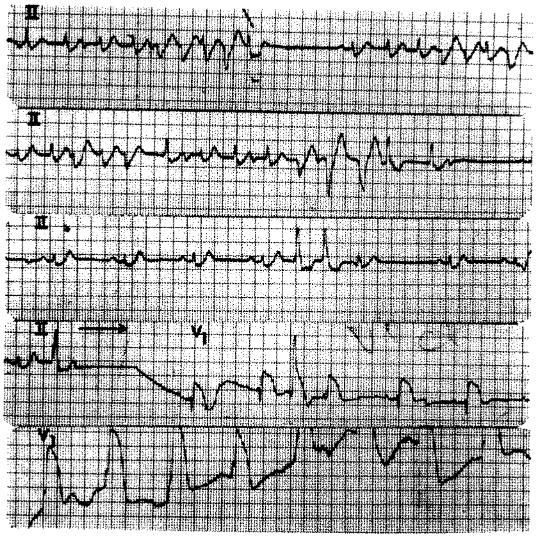

Fig. 2 *Rhythm strip obtained in the catheterisation laboratory during the first episode of angina. The lead was changed from II to V_1 in the 4th strip as noted. The tracings show sinus rhythm with ST segments consistent with acute ischaemic injury, alternating with sinus pauses and episodes of junctional and ventricular ectopic activity.*

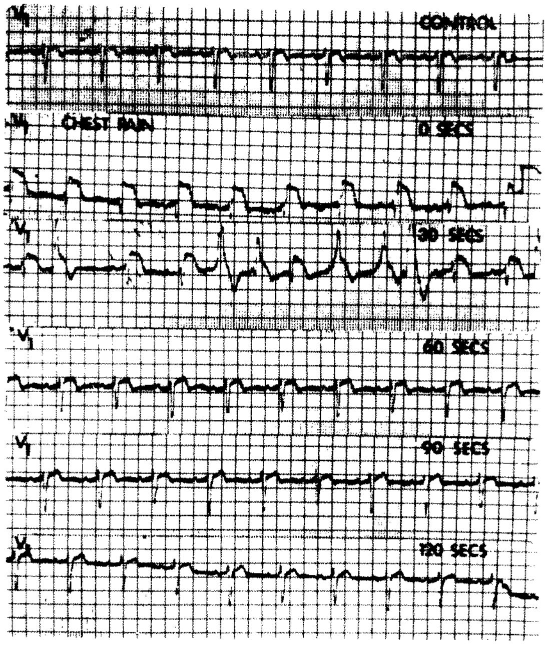

Fig. 3 *Non-continuous rhythm strips showing the time course of disappearance of ischaemic ST changes after administration of a 100 µg intravenous bolus of glyceryl trinitrate at time 0 seconds.*

an uneventful postoperative course. Fifteen months after operation he remains asymptomatic and has returned to work.

Discussion

This patient's clinical history, widespread typical electrocardiographic changes during chest pain, and severe proximal left anterior descending coronary artery stenosis suggest that superimposed coronary spasm resulted in ischaemia of a large region of the myocardium. The profound degree of coronary artery spasm demonstrated in several recent reports has been shown to result in conspicuous reduction, if not total obliteration, of coronary blood flow to a large segment of myocardium (Oliva *et al.*, 1973; Endo *et al.*, 1976). Recently, Maseri and co-workers (1978) have documented coronary artery spasm causing myocardial infarction when superimposed on vessels with a 90 per cent luminal stenosis.

Severe ischaemic injury to myocardial cells has been shown to result in ventricular arrhythmias. Bigger *et al.* (1977) have summarised the possible mechanisms of ventricular arrhythmias arising in the early (less than 15 minutes) arrhythmic phase of the Harris model of myocardial infarction in the dog. As a result of ischaemia, there is partial or complete inactivation of the fast inward sodium channel, raised extracellular potassium, lowered intracellular *p*H, and partial depolarisation of the injured cells. The action potentials generated by partially inactivated fast sodium currents and catecholamine enhanced slow inward calcium currents promote re-entry leading to ventricular tachycardia and ventricular fibrillation.

Conventional antiarrhythmic agents may have little, if any, success in controlling arrhythmias associated with acute ischaemia. Hope *et al.* (1974) have shown in the acutely ischaemic dog model that neither lignocaine nor procainamide was effective in reducing the time of onset of ventricular tachycardia after coronary occlusion. In a study of 2-hour-old canine infarcts, Kupersmith *et al.* (1975) showed that the beneficial effect of lignocaine in eliminating the dispersion of refractoriness between normal and ischaemic myocardium occurred with a delayed time course after drug administration. This lack of effectiveness of those agents may be the result both of an impairment of delivery to the ischaemic myocardium and inappropriate electrophysiological effects upon the ischaemic cells.

Our patient had received 200 mg subcutaneous lignocaine for local anaesthesia in addition to a continuous infusion of lignocaine at 1 mg/min and an acute intravenous bolus of 100 mg at the onset of ventricular tachycardia. Therefore, ventricular tachycardia recurred with myocardial ischaemia in spite of presumably high myocardial levels of lignocaine. The ability of intravenous glyceryl trinitrate to reverse coronary spasm (Schroeder *et al.*, 1977) and restore blood flow serves to eliminate many of the above pathological factors contributing to early phase ischaemia-induced arrhythmias, and probably contributed to rapid arrhythmia control in our patient. Epstein and colleagues (1973) reported dramatic improvement in arrhythmias when glyceryl trinitrate was administered in acute experimental or clinical myocardial infarction. Presumably as a result of increased myocardial perfusion the ventricular fibrillation threshold in acutely ischaemic dog hearts was increased, and the incidence of ventricular premature contractions in patients soon after admission to the coronary care unit with myocardial infarction was decreased (Epstein *et al.*, 1973, 1975).

Although other vasodilators such as nitroprusside have been shown to have directionally similar gross haemodynamic changes, glyceryl trinitrate has the advantage of increasing regional myocardial blood flow to ischaemic zones. This may occur through its greater vasodilator effect on large coronary conductance vessels as compared with small coronary resistance vessels (Chiariello *et al.*, 1976).

Glyceryl trinitrate is usually administered by the sublingual route. However, intravenous glyceryl trinitrate is probably more effective than the sublingual form of the drug in quickly controlling ischaemia-induced ventricular ectopic activity in view of its rapid onset of action (less than 60 seconds in this patient) because of prompt delivery of the drug to the coronary circulation. In addition, the ability to control the quantity and rate of drug delivery with an intravenous infusion offers distinct advantages. In this patient, a continuous intravenous infusion of glyceryl trinitrate was helpful in controlling ischaemia and arryhthmias for a prolonged period of time, allowing coronary arteriogrraphy to be performed safely. Further studies will be necessary to document its safety and effectiveness, but this agent seems particularly well suited for cases of coronary spasm encountered during angiography when it can be administered with careful electrocardiographic and haemodynamic monitoring, to control potentially life-threatening ischaemia and arrhythmias.

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Br Heart J 1980; **43:** 92–94

Double diastolic murmur in mitral stenosis with atrial fibrillation and complete heart block

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SUMMARY A double diastolic murmur was heard in a patient with mitral stenosis, atrial fibrillation, and complete heart block. Echo-phonocardiographic examination showed two separate opening and closing movements of the mitral valve in the same long diastole. A clear time relation was observed between the valve closing movements and the separate diastolic murmurs, giving support to the theory that the backward motion of the mitral valve against the forward blood flow through the valve is responsible for the production of these murmurs.

A few years ago, a new theory of the genesis of the mitral diastolic murmur was proposed, namely that the murmur resulted from impact between the forward mitral flow and the closing motion of the mitral valve (Criley *et al.*, 1971; Fortuin and Craige, 1973; Toutouzas *et al.*, 1974). This theory was challenged recently in an editorial by Tavel and Bonner (1976).

We are now reporting the unusual case of a patient with mitral stenosis, atrial fibrillation, and complete heart block, who had a double diastolic murmur, and in whom the role of the closing motion of the mitral valve in the genesis of the murmur was clearly demonstrated.

Case report

A 59-year-old woman entered hospital in September 1975 with a 2-month history of dizziness and syncopal attacks. She was not hypertensive and had never complained of dyspnoea or other symptoms of heart failure. Complete heart block was diagnosed

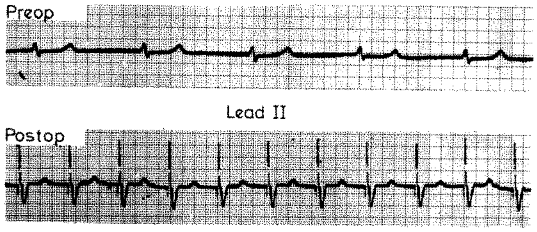

Fig. 1 *Lead II of the electrocardiogram before and during pacing. There are no P waves in either record.*

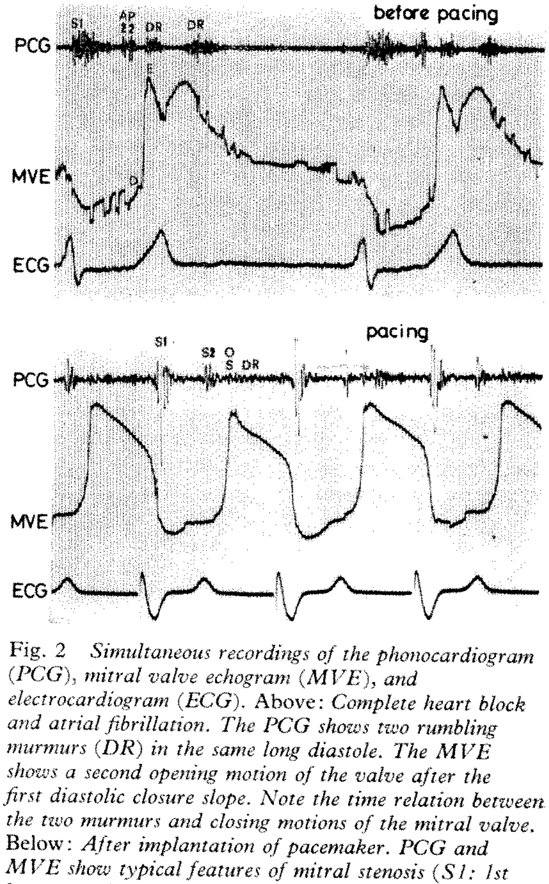

Fig. 2 *Simultaneous recordings of the phonocardiogram (PCG), mitral valve echogram (MVE), and electrocardiogram (ECG).* Above: *Complete heart block and atrial fibrillation. The PCG shows two rumbling murmurs (DR) in the same long diastole. The MVE shows a second opening motion of the valve after the first diastolic closure slope. Note the time relation between the two murmurs and closing motions of the mitral valve.* Below: *After implantation of pacemaker. PCG and MVE show typical features of mitral stenosis (S1: 1st heart sound, S2: 2nd heart sound, OS: opening snap).*

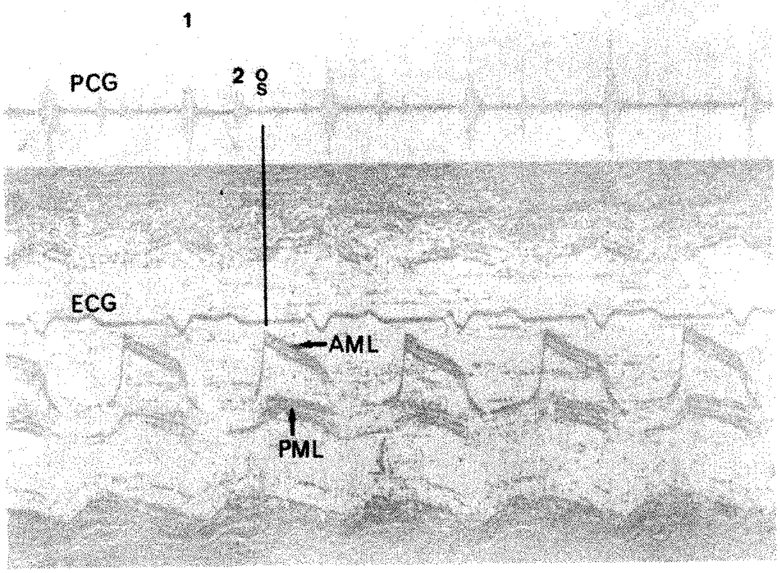

Fig. 3 *Recent echocardiogram with simultaneous phonocardiogram (PCG) and ECG lead II during pacing. The mitral valve echogram shows typical changes of mitral stenosis with anterior motion of the posterior mitral leaflet (PML). The PCG shows a distinct opening snap (OS), coinciding with the end of the rapid anterior mitral leaflet (AML) upstroke, and a diastolic murmur coinciding with the diastolic closure slope.*

on the clinical examination, and the electrocardiogram showed atrial fibrillation with an idioventricular rhythm at a rate of 35 per minute (Fig. 1). On *x*-ray examination the heart was moderately enlarged.

The clinical features of heart block were associated with an interesting auscultatory sign, a double diastolic rumbling murmur at the apex. This was confirmed by a phonocardiogram showing two separate murmurs during the same long diastole. The echocardiogram showed two distinct opening and closing movements of the mitral valve corresponding with the separate diastolic murmurs. Subsequently, a combined echo-phonocardiographic examination was carried out; the gated mitral valve signal from the Hewlett-Packard ultrasound device was recorded simultaneously with the phonocardiogram using an Electronics for Medicine multichannel recorder. We observed a clear time relation between the two closing motions of the mitral valve and the diastolic murmurs (Fig. 2). The patient was treated by a pacemaker implantation for the heart block. At a heart rate of 70 beats per minute, an opening snap and a single diastolic murmur were heard. The postoperative echo-phonocardiographic examination showed the typical pattern of mitral stenosis, with anterior motion of the posterior mitral leaflet, and again a time relation between the diastolic murmur and diastolic closure motion on the echocardiogram (Fig. 3).

Discussion

According to the new theory the mitral diastolic murmurs occur as the result of an impact between increased velocity of forward blood flow and the backward motion of the mitral valve (Fortuin and Craige, 1973; Toutouzas *et al.*, 1974). This theory explains some features of the diastolic murmurs in mitral stenosis, such as the absence of murmur before and a few milliseconds after the opening snap (Toutouzas *et al.*, 1974, 1978), the occasional presence of a presystolic murmur in atrial fibrillation (Criley and Hermer, 1971; Lakier *et al.*, 1972; Toutouzas *et al.*, 1974), and the low intensity or absence of the murmur in mitral stenosis with a calcified mitral valve. In addition, this theory accounts for the appearance of mid-diastolic murmurs well after the period of rapid filling in patients with mitral regurgitation or with congenital heart disease and a large left-to-right shunt (Fortuin and Craige, 1973). Finally, the closing motion of the mitral valve leaflets against the forward flow appears to be the cause of the Austin-Flint murmur in aortic regurgitation (Fortuin and Craige, 1972).

Complete heart block is occasionally associated with an apical mid-diastolic murmur. This has been attributed to increased blood flow across the mitral valve during the period of rapid ventricular filling and is louder when atrial contraction occurs at this time. However, in our patient with mitral stenosis and complete heart block, this explanation is insufficient. The second diastolic murmur was recorded well after the period of the rapid ventricular filling and, as the patient was in atrial fibrillation, atrial contraction could not be involved in the genesis of the murmur. Fig. 2 illustrates the clear time relation of the closing motion of the valve to the two separate murmurs observed during the same long diastole. The disappearance of the murmur after the F point of the echocardiogram and during the second opening motion of the valve, combined with reappearance of the murmur with the second closing valve motion, leaves little doubt about the important role of closing motion of the valve in its genesis. Thus, we find it very difficult to accept the theory of Tavel and Bonner (1976) who state that the diastolic murmur does not appear during the opening valve motions, 'since the mitral apparatus is moving forward with the atrioventricular blood during these periods', reducing mitral flow and turbulence.

The mechanism of the second opening of the mitral valve in our case is not known. It is likely that after the normal opening motion and subsequent closure, reopening results from increasing left atrial pressure during the long diastole.

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Br Heart J 1980; **43**: 95–98

Anatomical correction of transposition of great arteries with persistent ductus arteriosus

One year after operation

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SUMMARY The postoperative data are described of a boy who had a 'switch' operation for transposition of the great arteries with persistent ductus arteriosus more than a year before. The child is living a normal active life. Electrocardiography, echocardiography, and angiocardiography show persistent abnormality of structure and function of the right ventricle but no evidence of reduced coronary blood flow, coarctation at the suture lines of the great arteries, or aortic regurgitation. Reference is made to an identical case operated upon 2½ years ago.

During the past 2 years there have been several reports of the early results of the 'switch' operation in transposition of the great arteries (Jatene *et al.*, 1976; Ross *et al.*, 1976; Yacoub *et al.*, 1976; Kreutzer *et al.*, 1977) but detailed follow-up information beyond the early postoperative period is not available. We describe the clinical, angiocardiographic, and serial echocardiographic data obtained over the first postoperative year from a child whose transposition of the great arteries was corrected by this procedure.

Case report and surgical procedure

A baby boy was admitted to the Wilhelmina University Children's Hospital in Utrecht at the age of 2 months with cyanosis, dyspnoea, feeding difficulties, and other signs of right and left heart failure. After the diagnosis of transposition of the great arteries with persistent ductus arteriosus was established at cardiac catheterisation a balloon atrioseptostomy was performed. The heart failure was treated medically. The child made satisfactory progress until the age of 5 months when cardiac failure returned with hypoxia and metabolic acidosis. Cardiac catheterisation was repeated (Table). The ductus was still widely patent. M-mode echocardiography disclosed a well-developed and strongly contracting left ventricle. It was decided to switch the great arteries and close the ductus. The operation was carried out using cardiopulmonary bypass with reduced flow and a body temperature of 20°C on 10 May 1977. The ductus was closed at the start of the operation. The pulmonary trunk was situated directly behind the aorta and had a slightly larger diameter. The coronary arteries arose normally from the aorta, they were dissected down to 5 mm from their origin, removed together with a small button

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Table *Cardiac catheterisation data before and after the 'switch' operation*

	Oxygen saturation (%)						*Pressures (mmHg)*					
	RA	*RV*	*PA*	*LA*	*LV*	*Ao*	*RA*	*RV*	*PA*	*LA*	*LV*	*Ao*
Before	71	72		96	96	72	5	75/9	55/33	7	55/9	
After	78	76	78		96	96	5	50/5	44/20		87/10	87/50

RA = right atrium; RV = right ventricle; PA = pulmonary artery; LA = left atrium; LV = left ventricle; Ao = aorta.

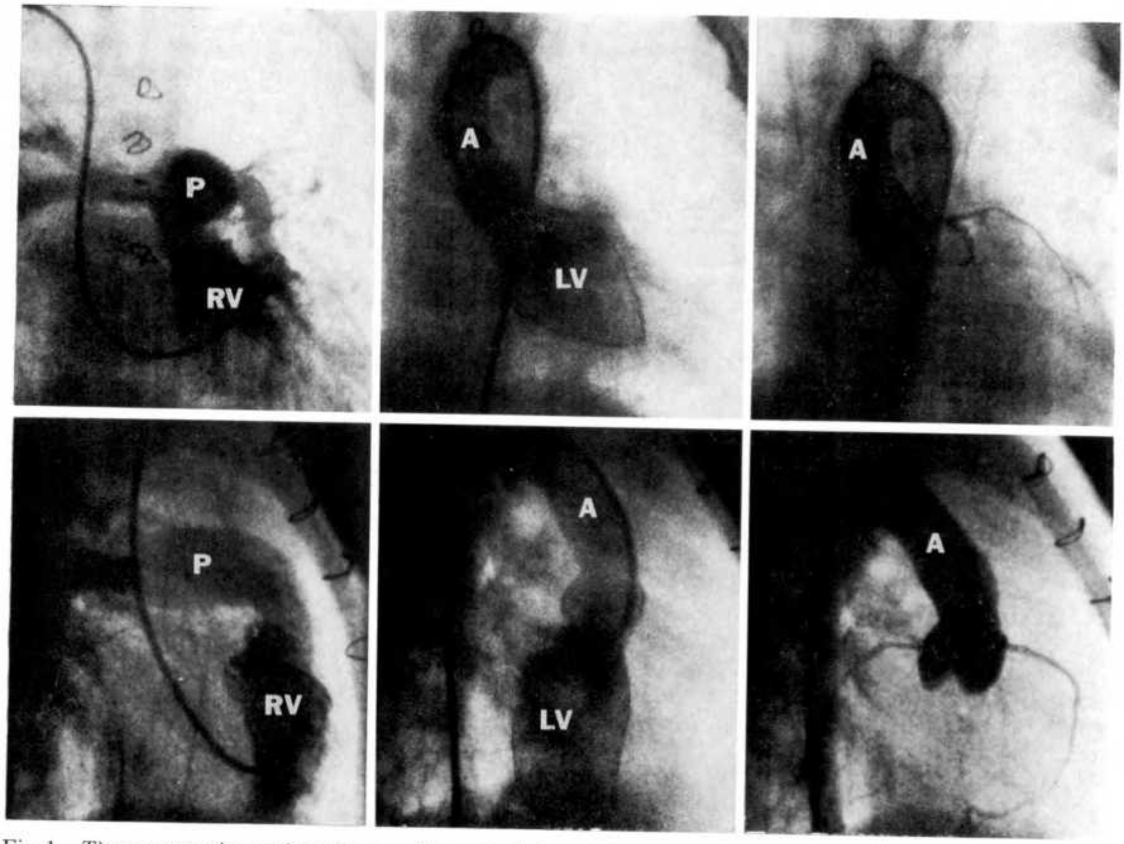

Fig. 1 *The postoperative angiocardiogram. Normal relation of the great arteries with the ventricles. No evidence of narrowing at the suture lines. The aortogram shows a competent aortic valve and filling of the coronary arteries appears to be normal. P, pulmonary artery; RV, right ventricle; LV, left ventricle; A, aorta.*

of aortic wall, and implanted into the side of the pulmonary trunk at sites previously marked with 6/0 prolene sutures. The aorta was divided as far proximally as possible at a level just above the right coronary artery ostium and the pulmonary trunk as far distally as possible just proximal to the bifurcation. The distal part of the aorta could thus easily be sutured to the pulmonary artery root, and a Medox prosthesis (internal diameter 16 mm) used to join the aortic root and the bifurcation of the pulmonary trunk. The holes in the aortic root left by the removal of the coronary arteries were also closed with the prosthesis. Rewarming was carried out during the anastoomtic procedure and the atrial septal defect was closed. At the end of bypass the heart was in sinus rhythm. The child made an uneventful recovery and was discharged after 3 weeks. Five months after operation cardiac catheterisation was repeated (Table). Angiocardiography (Fig. 1) showed that the right ventricle was still distinctly trabeculated. The pulmonary conduit was slightly dilated. The region of the suture lines in the aorta and the pulmonary artery showed no narrowing. The left ventricle had a normal appearance and the aortic valve was competent. There seemed to be good filling of the coronary arteries. More than a year later the child was taking no drugs and was thriving with his body weight and height at the 50th centile level. The electrocardiogram showed sinus rhythm, left ventricular preponderance, and no evidence of myocardial ischaemia. Twenty-four-hour ambulatory electrocardiographic tape monitoring showed no evidence of arrhythmias. There were still signs compatible with right ventricular hypertrophy but this had become less. Chest radiography showed mild to moderate cardiac enlargement and persistent plethora. On the M-mode echocardiogam the right ventricle remained enlarged but was clearly smaller than the well-developed left ventricle which was contracting well (Fig. 2).

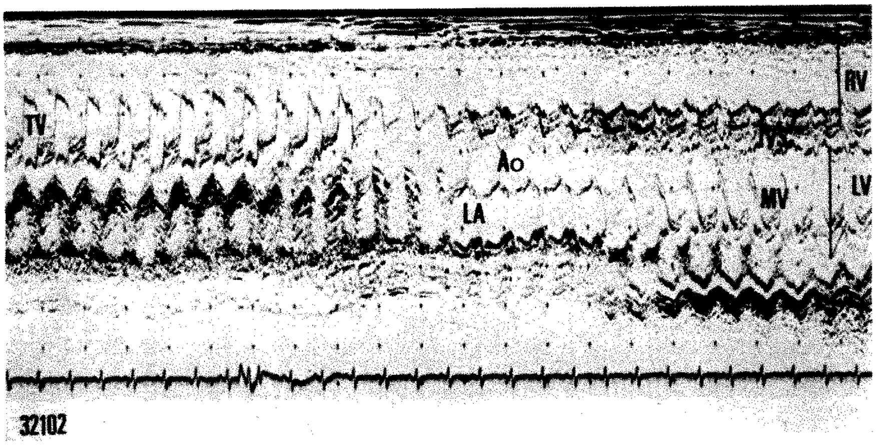

Fig. 2 *The postoperative echocardiogram. Note the normal dimensions and contraction of the left ventricle. The right ventricle is still enlarged. TV, tricuspid valve; LA, left atrium; Ao, aorta; MV, mitral valve; RV, right ventricle; LV, left ventricle.*

Discussion

The 'switch' operation is an anatomical correction of transposition of the great arteries and may avoid some of the late complications of the Mustard repair, for example the development of obstruction to systemic and pulmonary venous return (Stark *et al.*, 1974; Venables *et al.*, 1974; Gutgesell and McNamara, 1975). Arrhythmias are also likely to be less of a problem than with the Mustard procedure (El-Said *et al.*, 1972; Tynan, 1978). Certainly routine postoperative electrocardiograms and 24-hour ambulatory electrocardiographic tape monitoring of our patient, 14 months after operation, showed normal sinus rhythm and no arrhythmias. In contrast, too, the Mustard repair has no effect on the usual atrophy of the left ventricle in transposition of the great arteries (Silverman *et al.*, 1978), whereas in our patient postoperative angiocardiograms and echocardiograms showed normal left ventricular dimensions and contraction.

Other late problems of the Mustard repair, however, may be less avoidable. As the structure of the right ventricle is abnormal in transposition of the great arteries (Becú and Gallo, 1976), persistent abnormalities of its function should be expected, but since after the switch operation it becomes a low pressure ventricle, these abnormalities may at least occur less frequently than after the Mustard repair (Graham *et al.*, 1975). In our patient the postoperative right ventricular angiocardiogram continued to show an abnormal structure. Whether or not a progressive rise in pulmonary vascular resistance, sometimes observed after the Mustard repair (Rosengart *et al.*, 1975), will also occur after the 'switch' operation cannot be predicted. The risk is clear if pulmonary hypertension is present preoperatively, particularly if the operation is not undertaken at an early age. In this respect it is interesting that at recatheterisation after the 'switch' operation the pressure in the main pulmonary artery has been found to be either normal or much lower than preoperatively (Ross *et al.*, 1976; Kreutzer *et al.*, 1977; Abe *et al.*, 1978); in our patient it had fallen from two-thirds to one half of the systemic pressure.

Concern has been expressed about the likelihood of continued patency of the coronary arteries and the growth of the suture lines (Ross *et al.*, 1976). Postoperative angiocardiography in our patient was reassuring on these points and though the period between operation and cardiac catheterisation was relatively short it was a period of rapid growth for this child. The electrocardiogram showed no evidence suggestive of myocardial ischaemia.

Normally, in the presence of an intact interventricular septum the Mustard repair is still preferable to the 'switch' operation. Only if left ventricular pressure is close to systemic level can a 'switch' procedure be considered. In our case it was raised but only to two-thirds of the systemic pressure and many would have chosen the Mustard repair with division of the ductus, but because angiocardiography and echocardiography had shown a normally sized, well contractile left ventricle with a well-developed wall we opted for the switch operation. So far, the choice seems to have been justified.

One of our first patients in whom a 'switch' operation was performed also had an intact ventricular septum and a persistent ductus arteriosus (Ross *et al.*, 1976)—a 20-month-old girl. Unfortunately, as she lives abroad full follow-up information is not available but it appears that 2½ years after operation this girl is also living a normal active life without complications (J. Somerville, 1978, personal communication).

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Addendum

Since submission of this paper, the boy is still thriving. Right ventricular dimension has been further reduced. Whereas the LV/RV rate was 1·4:1 on the M-mode scan one year after the 'switch' (Fig. 2) it was 2·7:1 at the end of the second postoperative year. Recent electrocardiograms show less right ventricular activity with normal left ventricular preponderance.

Br Heart J 1980; **43:** 99–123

Proceedings of the British Cardiac Society

THE AUTUMN MEETING of the British Cardiac Society was held at the Wembley Conference Centre on Thursday and Friday, 1 and 2 November 1979. The President, W SOMERVILLE, took the Chair during private business. At the scientific sessions the Chair was taken by LAWSON MCDONALD.

Abstracts of papers

YOUNG RESEARCH WORKERS AWARD

Tissue acidosis in myocardial ischaemia

S M Cobbe
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The significance of acidosis in ischaemic heart muscle was investigated in isolated rabbit myocardium, in open-chested dogs, and in patients with coronary artery disease. A needle and catheter tip electrode were designed and developed for continuous recording of myocardial tissue pH in animals, and of intravascular pH in the canine and human coronary sinus.

In isolated rabbit myocardium tissue pH fell within five seconds of the onset of ischaemia; the fall after 30 minutes ischaemia was more than 1 pH unit. In dogs, during 150 seconds of coronary occlusion a rapid fall in tissue pH also occurred, but coronary venous pH was almost unchanged. On reperfusion, however, there was a large transient fall in coronary venous pH caused by washout of hydrogen ions from the tissue.

Coronary sinus and arterial pH were continuously monitored during and after atrial pacing in 20 patients. In nine patients with evidence of ischaemia on pacing, coronary sinus pH fell during pacing ($P<0{\cdot}001$), but the greatest fall was in the 30 seconds after the end of pacing, analogous to the washout seen in dog experiments. Coronary sinus pH did not fall in patients without ischaemia ($\chi^2=11{\cdot}4$, $P<0{\cdot}001$).

Tissue acidosis can account for most of the early fall in contractility during myocardial ischaemia. Continuous measurement of coronary sinus pH during and immediately after atrial pacing gives direct evidence of ischaemia in man.

Improvement of electrocardiogram by chronic beta adrenoceptor blockade during healing phase of clinical and experimental myocardial infarction

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I have developed a new technique for praecordial electrocardiographic mapping to quantify ischaemic myocardial damage and validated it by showing a correlation ($r=0{\cdot}827$ and $r=-0{\cdot}623$) between the maximum ΣQ and minimum ΣR from the map compared with the cumulative release of CK MB in 28 patients with anterior myocardial infarction. The reproducibility of the technique was studied under a wide variety of conditions.

Mapping was then used to study the evolution of the electrocardiogram in the chronic healing phase in 22 patients with acute myocardial infarction randomised to receive atenolol or placebo for 12 months. A significantly greater recovery of ΣR wave and disappearance of ΣQ was observed in the treated group compared with those on placebo ($2p<0{\cdot}001$ and $2p<0{\cdot}025$, respectively).

A further group of 67 patients with acute myocardial infarction randomised between metoprolol and placebo were studied using standard 12 lead electrocardiograms. This showed that the return to normal of the electrocardiogram was related to slow heart rates either spontaneous or induced by beta-blockers. An initial small infarct was found to be associated with improved recovery on the electrocardiogram.

I have also shown improved recovery on electrocardiogram with atenolol in 14 dogs after acute myocardial infarction.

I have evidence that these changes are not the result of intraventricular conduction defects, bradycardia *per se*, left ventricular hypertrophy, or cardiac dilatation. It may be a result of improved healing or shrinkage of myocardial scar tissue.

Relation of ventricular arrhythmias to primary ventricular fibrillation

R W F Campbell
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Potential 'warning arrhythmias' for primary ventricular fibrillation were sought in the continuously recorded electrocardiograms of two groups—17 patients who developed primary ventricular fibrillation and 21 similar patients who did not. None had received antiarrhythmic therapy in the preceding 72 hours. Electrocardiographic analysis up to the twelfth hour after infarction was performed by three independent observers and employed a specially developed computer system. An R-on-T ventricular ectopic complex ($QR'/QT \leqslant 0{\cdot}85$) initiated all episodes of ventricular fibrillation but initiated only 1·5 per cent of episodes of ventricular tachycardia (4 of 265). The time course of R-on-T complexes differed from other ventricular arrhythmias including ventricular tachycardia, but closely paralleled the pattern of ventricular fibrillation. One or more R-on-T complex were recorded in 11 patients in each group. A mean prevalence of $\geqslant 1/1000$ minutes of electrocardiogram occurred in eight patients with ventricular fibrillation and only one patient without ventricular fibrillation. In the 10 minutes before ventricular fibrillation the group incidence of R-on-T complex showed a striking increase.

The different time relation of R-on-T complexes and other ventricular arrhythmias and the prevalence and change of prevalence of R-on-T complexes, while not of practical value in predicting ventricular fibrillation, may contribute to our knowledge of the genesis of ventricular arrhythmias in acute myocardial infarction.

Relation of ventricular ectopic beat frequency to heart rate and everyday physical activity

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A method has been developed to study the effect of heart rate and of everyday physical activity on the ventricular ectopic beat frequency of patients monitored within six weeks of a myocardial infarction. The technique involves a computer analysis of 24-hour recordings of electrocardiogram and walking activity, and this study was based upon 49 such recordings, throughout all of which the ectopic beats were shown to be correctly identified by computer. A statistically significant relation between ectopic beat frequency and heart rate was shown in 39 (80%) of these recordings, with 24 having ectopic beats predominantly at the lower heart rates and 15 at the higher heart rates. Similarly, walking activity affected ectopic beat frequency in 14 (74%) of the 19 patients studied after discharge from hospital and the response to activity reflected the response to heart rate.

All the patients whose ectopic frequency increased at the higher heart rates were still alive one year after being studied and there was only one cardiac death among the patients with bradycardia-related ectopic beats. It therefore seems unlikely that either type of response of ectopic frequency to heart rate carries a particularly adverse prognosis.

Non-invasive assessment of diastolic function in hypertrophic cardiomyopathy on and off beta-adrenergic blocking drugs

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Beta-adrenergic blocking drugs in hypertrophic cardiomyopathy provide symptomatic relief but their effect on long-term prognosis is uncertain.

Thirty patients have been studied non-invasively by simultaneous recordings of echocardiogram, apex cardiogram, phonocardiogram, and electrocardiogram in order to assess diastolic abnormalities on and off oral beta-adrenergic blocking drugs. While on treatment all these patients had a mean dose of propranolol of 200 mg/day and the drug was stopped for one week before repeating the non-invasive studies for assessment off treatment. The following indices were studied; isovolumic relaxation period (A_2 to mitral valve opening), relaxation period (A_2 to 'O' point of apex cardiogram), peak left ventricular filling rate, and the duration of the rapid filling phase.

Prolonged isovolumic relaxation period and relaxation period reflect a reduced rate of fall of left ventricular pressure and in this study both isovolumic relaxation period and relaxation period were shortened in seven and prolonged in 10 patients. Eleven patients showed inconsistent results and two remained the same after propranolol. Most of the patients had a prolonged isovolumic relaxation period and relaxation period before propranolol. The alteration in the peak left ventricular filling rate and the duration of the rapid filling phase will be discussed.

It is concluded that the response of diastolic indices to beta-blocking drugs in hypertrophic cardiomyopathy is variable and that there is a group of patients who improved their diastolic function with beta-blocking drugs.

Changes in QRS amplitude during maximal exercise testing and relation to presence of coronary artery disease and left ventricular dysfunction

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To test the theory that QRS amplitude varies with change in ventricular volume, changes in R wave amplitude were measured sequentially during and after 12 lead maximal treadmill exercise in 62 patients with coronary artery disease and 14 normal subjects. At maximal exercise R wave amplitude increased in patients with coronary artery disease by 2·4 (±0·3) mm and in normal subjects decreased by 3·2 (±0·4) mm. In addition to differential amplitude changes recovery time was delayed in patients with coronary artery disease and left ventricular dysfunction, being 8·6 (±0·8) minutes in patients with three vessel coronary artery disease and left ventricular dyskinesis or akinesis, 3·9 (±0·7) minutes in patients with single vessel coronary artery disease, and 3·0 (±0·6) minutes in normal subjects. Increase in R wave amplitude was greatest in patients with akinesis or dyskinesis (3·5±0·5 mm) compared with those with localised hypokinesis (2·3±0·3 mm). Increase in R wave amplitude was an independent indicator of coronary artery disease with no correlation between regional R wave changes and areas of ischaemia on the 12 lead exercise electrocardiogram.

Changes in R wave amplitude and behaviour may distinguish patients with coronary artery disease from normals and provide a non-invasive marker of left ventricular dysfunction.

Further experience with anatomical correction of simple transposition of the great arteries

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Between 1975 and 1979, 33 patients underwent anatomical correction of transposition of the great arteries. Of these, 14 aged between 1 month and 2·5 years had simple transposition and underwent two-stage anatomical correction. After the first stage operation of pulmonary artery banding the peak systolic left ventricular pressure rose from 32±12 to 80±30 mmHg with no significant change in end-diastolic pressure or ejection fraction. This was associated with decrease in actual pulmonary flow, but no change in effective pulmonary flow.

Correction was performed four weeks to eight months (mean three months) later. There were four early deaths and no late deaths (follow-up from three to 36 months). After an initial period of cardiac failure the remaining 10 patients became asymptomatic with normal development. Rapid change in electrocardiogram, vectorcardiogram, and echocardiogram towards normality was observed. Repeat cardiac catheterisation was performed in seven, three weeks to two-and-a-half years after operation. Left ventricular ejection fraction was normal in all, mild mitral regurgitation was present in two investigated early, minimal aortic regurgitation in four, and moderate supravalvar pulmonary stenosis in one. The aortic and coronary anastomoses appeared to grow normally.

Pulmonary blood supply in pulmonary atresia with ventricular septal defect and multifocal pulmonary blood supply

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We have previously shown by examination of necropsy material in patients with pulmonary atresia and ventricular septal defect with multifocal pulmonary blood supply that the hypoplastic central pulmonary arteries frequently connect to a minority of the 19 broncopulmonary segments, and we suggested that this would limit the effectiveness for surgery. In order to see whether these findings were biased by virtue of the patients having died, we reviewed the pre- and postoperative angiocardiograms, including selective collateral injections, in nine patients who survived a shunt operation.

Central pulmonary arteries were present in six patients and absent in three. Insertion of a shunt to a central pulmonary artery in five cases improved perfusion in only six to seven segments of lung per case. In the remaining four cases, a shunt into an intrapulmonary artery, connected to a collateral, increased perfusion to three to eight segments of each lung. Central and lobar pulmonary arteries appeared larger, but stenoses within and between these vessels were frequent and the peripheral vessels continued to appear abnormally small.

We conclude that in a high proportion of cases, the total pattern of pulmonary vascular supply will preclude satisfactory total repair unless present management techniques are improved.

Risk factors after balloon atrial septostomy in patients with complete transposition

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Despite balloon atrial septostomy, some patients with complete transposition of the great arteries die before reaching elective definitive surgery in the second six months of life. To discover why, we analysed the fate of 144 patients who had had balloon atrial septostomy since 1966, using a modified logrank survival test with multivariate capability. Patients were withdrawn alive on reaching definitive surgery.

The following largely independent factors were associated with a statistically significant ($P < 0.05$) excess mortality: pulmonary hypertension, the presence and size of ventricular septal defect or persistent ductus arteriosus, relative anaemia, absence of left ventricular outflow tract obstruction, low arterial oxygen saturation, aortic stenosis and coarctation, and balloon atrial septostomy between one week and one month of life.

Those of the above factors that can be determined at balloon atrial septostomy or routine three-month cardiac catheterisation were then introduced into discriminant function analysis on survival to six months. Hence the probability of any individual patient dying in the first six months was calculated, allowing for these factors. This prediction was correct in 72 per cent of the patients studied. By offering earlier definitive correction to patients thus identified as at high risk of premature death, it should prove possible to reduce overall mortality in transposition of the great arteries.

Atrial filling characteristics after the Mustard and Senning procedures: analysis by transcutaneous Doppler ultrasound

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Venous inflow correction of transposition of the great arteries involves construction of an interatrial baffle, which may consist either of living atrial tissue (Senning's operation) or pericardium/Dacron (Mustard's procedure).

To investigate whether this difference might affect atrial compliance and/or volume we recorded jugular venous waveforms in 24 patients operated on in Leiden, eight after Mustard's operation and 16 after Senning's. No patient had caval pathway obstruction.

Normal children display waveforms exhibiting two forward flow maxima of roughly equal height, one of atrial filling during ventricular systole and the other of ventricular filling.

After Mustard's operation, peak and total flow during atrial filling were reduced to a mean of 45 and 23 per cent of the ventricular filling phase, respectively. After Senning's operation these values were significantly higher, being 61 per cent ($P < 0.05$) and 44 per cent ($P < 0.001$), respectively.

Since the composition of the two groups was identical with regard to the mitral valve status and left ventricular pressure load, we conclude that this observed difference reflects a difference in atrial filling characteristics. The Senning operation appears to allow easier atrial filling because the living interatrial baffle is more compliant, and possibly also because the new systemic venous atrium is larger.

Surgical repair of common atrioventricular orifice without atrial septal defect in two patients

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Atrioventricular canal defects define a spectrum of cardiac malformations characterised by an aortic valve unwedged between the atrioventricular valves and a 'scooped-out' appearance of the interventricular septum. We distinguish between complete and partial forms on the basis of a common or partitioned atrioventricular orifice. Recently, we operated upon two cases of complete atrioventricular orifice without an ostium primum interatrial septal defect. In both, there was a common atrioventricular orifice with the anterior common leaflet bridging the interventricular septum and attached to one papillary muscle in the right ventricle. There was a wide interventricular communication. The interatrial septum was well formed; its secure attachment to the superior edge of the anterior and posterior common leaflets prevented any interatrial communication. In both cases it was necessary to resect the inferior border of the interatrial septum in order to visualise the leftward components of the two bridging leaflets. The surgical repair of the thereby created complete atrioventricular canal Rastelli type C, was then carried out as usual by repair of the left atrioventricular valve and patch closure of the atrioventricular communication. Both patients are well three and five months after operation, though residual mitral regurgitation needed reoperation in one.

Common atrioventricular canal: late results after surgical repair

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Nine patients, aged 23 months to 39 years, operated on from 1964 to 1977 in the National Heart Hospital, left hospital after repair for common atrioventricular canal and have had complete follow-up with recatheterisation. Six had earlier palliative surgery: banding of the pulmonary artery (4), Waterston (1), Blalock anastomosis (1). The right ventricular pressure was systemic in seven and below in two with an unusual small canal defect.

During the follow-up period of two to 14 years, one died suddenly 14 years later having had no residual haemodynamic lesion but with changing bundle-branch block and prolongation of the PR interval with periods of asymptomatic bradycardia. The other eight had mitral regurgitation, mild in six, moderate in one, and severe in one whose calcified mitral valve was replaced eight years later.

The PR interval has increased in all but one who has had syncope associated with Wenckebach and ventricular tachycardia requiring pacing and propranolol 11 years after operation. No other rhythm disorder has occurred. The pulmonary artery pressure and resistance fell in all. One had a small ventricular septal defect. None had subaortic gradients.

The careful, long-term follow-up of patients with repaired common atrioventricular canal demonstrates good symptomatic and haemodynamic results but the conducting tissue and mitral valve function may continue to cause problems.

Interaction between cigarettes and propranolol in treatment of angina pectoris

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This study investigates whether cigarette smoking interferes with the medical management of angina pectoris. Ten patients with angina pectoris who smoked at least 10 cigarettes a day were studied by recording heart rate, blood pressure, and 16 lead praecordial electrocardiographic maps before and after a standardised maximal exercise test at the end of four randomly allocated two-week treatment periods. These periods were (a) on glyceryl trinitrate (GTN) off smoking, (b) on GTN while smoking, (c) on GTN and propranolol (240 mg daily) off smoking, and (d) on GTN and propranolol while smoking. Carboxyhaemoglobin was measured to ensure compliance. On GTN and off smoking the maximum heart rate achieved was 137 to 156 beats a minute, the maximum systolic blood pressure was 160 to 210 mmHg, and the maximum area and severity of ST segment changes was two to eight positions and 3 to 12 mm, respectively. An analysis of variance comparing the four groups showed that smoking was associated with a significantly higher heart rate, blood pressure, number of positions with ST segment depression, and total ST segment depression after exercise ($P < 0{\cdot}01$). This also occurred when patients were on propranolol ($P < 0{\cdot}01$). These results suggest that smoking aggravates the simple haemodynamic indices that are used to assess myocardial oxygen requrements and the exercise induced praecordial electrocardiographic signs of myocardial ischaemia. These effects were still evident after treatment with propranolol and represent a hindrance to the effective medical treatment of angina pectoris.

Propranolol in acute myocardial infarction

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Thirty patients with apparently uncomplicated anterior myocardial infarction were considered for randomisation into a trial of oral propranolol 40 mg three times daily or placebo. The patients were studied within eight hours after the onset of their cardiac pain. A Swan-Ganz thermodilution catheter was used to measure both the pulmonary capillary wedge pressure and the cardiac output. Plasma catecholamines—noradrenaline and adrenaline, were measured. Five patients who had an 'inappropriate' tachycardia were found to have a significantly elevated pulmonary capillary wedge pressure of 21±4 mmHg and were not given propranolol. In the propranolol group of patients heart rate fell from 87±15 to 76±9 beats/min ($P<0{\cdot}01$) as did cardiac output from 4·9±0·7 to 4·5±0·9 l/min ($P<0{\cdot}05$). There was no change in the wedge pressure 14±2 and 13±2 mmHg but mean systemic blood pressure fell from 103±10 to 98±10 mmHg. Plasma catecholamines, particularly noradrenaline, increased from 0·26±0·5 to 0·44±0·7 ng/ml. The haemodynamics did not change in the placebo group but plasma noradrenaline fell from 0·44±0·66 to 0·32±0·56 ng/ml. Four patients developed cardiac failure of whom three were receiving propranolol. These results suggest that 'inappropriate' tachycardia indicates left heart failure and that propranolol cannot safely be given to patients with an apparently uncomplicated anterior myocardial infarction. Propranolol also appears to increase plasma catecholamines in this group of patients.

Ergometrine induced 'angina'—a diagnostic pitfall

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We have reviewed patients diagnosed as having cardiac pain but normal coronary arteriograms and have fully reinvestigated those with persistent and convincing symptoms. A small group of patients has been identified who have typical cardiac pain which occurs at rest and with exertion, can be induced by coronary sinus pacing or by ergometrine, may be associated with T wave inversion, and is relieved by nitrites. These patients showed no evidence of any cardiac abnormality and again had structurally normal coronary arteriograms, transmyocardial arteriovenous lactate differences remaining normal with pacing or with ergometrine to the point of 'angina' in every case. Oesophageal manometry, however, showed that the ergometrine-induced 'angina' was associated with the development of oesophageal spasm. No oesophageal spasm was seen in these or other patients given ergometrine in the absence of pain.

This study shows that 'angina' induced by ergometrine cannot be regarded as necessarily indicating coronary artery spasm. The ergometrine test may be useful in establishing a positive diagnosis of oesophageal spasm in this diagnostically difficult group.

Verapamil in chronic stable angina—controlled study with quantified treadmill exercise and computer analysed ST segment changes

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The antianginal efficacy of verapamil hydrochloride in a dose of 120 mg three times daily was assessed by serial continuous multistage exercise and on-line computer assisted ST segment analysis. Twenty-seven patients with confirmed effort-induced angina were evaluated by a double-blind placebo controlled cross-over study. Maximal treadmill tests were performed before treatment, two weeks after placebo, and two and four weeks after 360 mg daily of verapamil. Indices included angina attacks, consumption of glyceryl trinitrate, anginal time (time taken to develop angina on treadmill testing), cumulative ST depression, time taken to develop 1 and 2 mm ST change, and ST indices (cumulative ST depression corrected to time of exercise, oxygen consumption, METS equivalent, and workload). Thirteen patients became angina free after two weeks and 15 angina free after four weeks treatment. The treadmill exercise time increased from 6·6±0·4 minutes to 11·0±1·0 minutes ($P<0{\cdot}001$). Pronounced improvements were observed at statistically significant levels ($P<0{\cdot}001$) in trinitrin consumption, 1 mm time, 2 mm time, double product, heart rate response to exercise, cumulative ST depression, and ST units. Side effects consisted of constipation in seven, prolonged PR interval in two, and headache in one. None of the patients developed signs of cardiac failure. These results indicate that verapamil in a dose of 360 mg daily is a very powerful antianginal agent free from troublesome side effects.

Coronary haemodynamic effects of nifedipine: comparison with glyceryl trinitrate

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To determine the coronary haemodynamic effects of nifedipine, values for myocardial blood flow (coronary sinus flow—CSF), myocardial oxygen extraction (O_2 extr), and myocardial oxygen consumption (MVO_2) were obtained in sinus rhythm (SR) and during rapid atrial pacing (RAP) at rates insufficient to produce angina in 11 patients undergoing cardiac catheterisation for suspected coronary artery disease. In the patients with demonstrated coronary artery disease rapid atrial pacing rate was increased to produce angina. Measurements were repeated after 20 mg nifedipine sublingually. Results were compared with a group of patients who received 0·5 mg glyceryl trinitrate (GTN) sublingually.

In sinus rhythm, nifedipine reduced mean O_2 extr from 62 to 54 per cent (13%, $P<0{\cdot}02$) with no significant change in CSF or MVO_2. GTN reduced mean CSF from 171 to 115 ml/min (33%, $P<0{\cdot}02$) and MVO_2 from 19·9 to 12·3 ml/min (38%, $P<0{\cdot}01$), with no significant change in O_2 extr.

During rapid atrial pacing, nifedipine reduced mean O_2 extr from 59 to 54 per cent (8%, $P<0{\cdot}05$), with no significant change in CSF or MVO_2. GTN reduced mean CSF from 207 to 168 ml/min (19%, $P<0{\cdot}05$) and MVO_2 from 24 to 18·2 ml/min (24%, $P<0{\cdot}05$) with no significant change in O_2 extr.

A major effect of nifedipine was coronary vasodilatation whereas GTN reduced MVO_2 with no apparent coronary vasodilator effect.

Both drugs were effective in relieving pacing-induced angina, probably by different mechanisms.

M-mode subxiphoid echocardiographic scan in analysis of atrioventricular junction

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Analysis of the atrioventricular junction is important for sequential diagnosis in congenital heart disease. It is necessary to know (i) if one or both atria connect to the ventricular mass; (ii) if both connect, whether the ventricular inlets are separated; (iii) how many valves guard the junction; and (iv) the relations of these valves to the inlet ventricular septum. The usefulness of parasternal M-mode echocardiography is limited because of difficulty in profiling the inlet septum. Theoretically, a subxiphoid approach should provide this information. This study assessed its practical advantages and developed a composite subxiphoid scan in which the transducer beam is initially directed from the subxiphoid notch to cross right ventricular cavity, right atrioventricular orifice, and aorta. With subsequent sinistroposterior beam angulation the relations of right aortic wall and atrioventricular valves to the inlet septum are shown.

The scan was assessed in 30 normal children, 47 with atrioventricular defects and nine with univentricular hearts of left ventricular type, three with double inlet, and six with absent right atrioventricular connection. In all abnormal hearts the scan accurately predicted the atrioventricular junction anatomy found at surgery or angiography, suggesting that the subxiphoid scan is the technique of choice when studying the inlet septum.

Ventricular morphology—two-dimensional echocardiographic recognition in complex congenital heart disease

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Definition of ventricular morphology and their relations is mandatory in the diagnosis of complex congenital heart disease. Based on experiences in over 1000 studies of patients with normal cardiac connections, two-dimensional echocardiographic criteria for right (RV) versus left ventricular (LV) morphology were compared in 16 patients, all of whom had two ventricular chambers; biventricular angiography demonstrating transposition of the great arteries (TGA) in three, corrected TGA in 10, anatomically corrected malposition in one, and a 'criss-cross' heart in two. Criteria used for RV morphology were: insertion of chordae tendineae into interventricular septum; the presence of an infundibulum; the presence of trabeculated endocardium and a moderator band. Criteria for LV morphology were: the presence of two discrete papillary muscle groups and a smooth endocardium. Because of the invariable association of the AV connection with the respective ventricle attention was given to AV valve morphology, its attachment to the interventricular septum, and its cusp number.

In all patients with a posterior LV, two papillary muscle groups were seen. These were also observed in the anterior morphological LV in five of the 10 patients with corrected TGA, though the posterior ventricle was correctly identified as having RV morphology in all 10 patients by chordae inserting into the interventricular septum. Identification of infundibulum, the appearance of endocardium, and the presence of a moderator band were not useful as criteria. Correct identification of AV valve morphology was made in all 16 patients studied. Though the ventricular insertion of chordae may recognise the RV and LV, correct prediction of ventricular morphology was best achieved by identifying the associated AV valve.

Diagnostic accuracy of two-dimensional echocardiography in cyanosed infant

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Real-time two-dimensional echocardiography (60° mechanical sector scanner) has been applied to the preliminary assessment of a consecutive series of 59 infants (ages 14 hours to 6 months, weights 2·1 to 5·8 kg) suspected of having congenital heart disease and subjected to cardiac catheterisation. The basic diagnosis was correctly established with two-dimensional echocardiography in all those with transposition of the great arteries (16), pulmonary valve atresia or severe stenosis (5), left heart hypoplasia (4), Fallot's tetralogy or Fallot-type pulmonary atresia (5), atrioventricular canal (3), and truncus arteriosus (2). In six of seven infants with single ventricle the anatomy was correctly ascertained, and in four patients with complex anomalies the echocardiogram gave useful information though not the full diagnosis. The echocardiogram was misinterpreted in one infant with severe pulmonary hypertension and in one with total anomalous pulmonary venous drainage (TAPVD). No two-dimensional echocardiographic abnormality was found in the other patients with pulmonary hypertension (3) or in patients with respiratory disease (2). TAPVD was strongly suspected but not diagnosed with certainty in four. In two, the quality of the two-dimensional image was inadequate for diagnostic assessment. Two-dimensional echocardiography provides a rapid anatomical diagnosis in most cyanotic infants. With further experience of the technique even more reliable diagnostic interpretations are probable.

Long-term oral prostaglandin E_2 in ductus dependent pulmonary circulation

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Short-term intravascular prostaglandin E_1 or E_2 (PGE_1 or PGE_2) effectively maintains ductus arteriosus patency in neonates whose pulmonary circulation is ductus dependent. We have evaluated oral PGE_2 administration in seven infants with pulmonary atresia or tricuspid atresia, in five of whom the pulmonary arteries were initially considered too small for anastomotic operations. PGE_2 was given orally, 30 to 250 μg hourly to four-hourly, for six days to four months with repeated measurements of arterial oxygen tension (PaO_2) or saturation (SaO_2). Discontinuing treatment for two to eight hours in individual cases caused PaO_2 or SaO_2 to fall by 25 to 35 per cent of the values achieved on treatment; they rose again as early as 15 minutes after an oral dose. These changes were closely related to plasma PGE_2 concentrations measured by radioimmunoassay. Satisfactory levels of SaO_2 ($>65\%$) could be maintained only while treatment continued. Three infants, recatheterised four to 10 weeks after starting PGE_2, showed growth of pulmonary arteries. Aortopulmonary shunts, attempted in five infants, have been successful in four. The effectiveness and relative simplicity of oral PGE_2 treatment suggest that it may supersede intravascular infusions for both short- and long-term purposes.

Fetal tachycardia

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The incidence of fetal arrhythmias is not known but the few reports suggest that it is seldom recognised. We are reporting three infants who were delivered by emergency caesarean section because they had persistent tachycardia. Two were cyanosed at birth, case 1 because of transposition of the great arteries and case 3 because of persistence of the fetal circulation. Cases 2 and 3 did not have a congenital cardiac defect.

The three infants presented with atrial flutter. The first infant could not be converted to sinus rhythm by drug therapy or DC conversion and died at one week from aspiration, despite a successful atrial septostomy. The second infant was also refractory to treatment but well compensated and reverted spontaneously to sinus rhythm by 2 months of age. The third patient was easily converted to sinus rhythm by DC countershock.

Necropsy on case 1 showed a hypoplastic sinus node represented by a small area of cells with increased fibrous tissue. These findings suggested that this infant could not have reverted to sinus rhythm while the other two infants probably represented delayed maturation of the sinus node.

Our findings show that persistent fetal tachycardia may be the result of an abnormal rhythm and that histological examination of the conducting tissue in other fatal cases may be helpful in understanding the mechanism of tachycardias in the fetus and neonate.

Quantitative dynamic study of distribution of thallium-201 in normally perfused, ischaemic, and infarcted myocardium

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Time-dependent regional distribution of thallium-201 was measured by serial imaging for 24 hours after injection during maximal exercise. Normal myocardium showed peak activity 30 minutes after injection followed by an exponential decline independent of decay of the isotope. Infarcts reached peak activity at the same time, but never exceeded 50 per cent of the highest activity in normal myocardium.

Counts recorded represent the activity of a cylinder formed by two walls and the cavity of the ventricle. The activity is a composite of the infarcted zone and overlying, or underlying, normal myocardium. Subtraction of the normal activity curve from the infarct curve shows that all activity is obtained from normally perfused muscle; the infarct contributes only as an inactive 'window'.

Ischaemic myocardium showed delayed uptake reaching a peak one-and-a-half hours after injection and maintaining that level of activity until equal to the falling activity of adjacent normal muscle. If the contribution of superimposed normal myocardium is subtracted, ischaemic muscle is shown to accumulate thallium-201 for four to six hours before reaching a peak and then declining at a similar rate to normal muscle.

The findings are important in interpreting thallium-201 scintigrams and may facilitate the identification of preclinical ischaemia.

ECAT imaging in acute myocardial infarction

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Recent developments in emission computed tomography (ECAT) allow cross-sectional three-dimensional imaging of the heart. This overcomes the superimposition of anatomical 'non-interest' regions of conventional scanning. The images reflect quantitatively the distribution of the radioactive indicator concentration in the myocardium and thus provide a potential means of quantifying regional myocardial perfusion and necrosis.

We have evaluated the suitability of ^{99m}Tc-IDP imaging in acute infarction with a transaxial emission tomography device (slice time five minutes) and compared it with standard scintigraphy in 20 patients. Though of similar sensitivity, the tomographic approach in the ECAT sections offers an opportunity for quantification of infarct size and this is the significant clinical potential of the technique. In addition, the difficult diagnosis of subendocardial infarction appears to benefit from the improved contrast in the ECAT sections.

Correlation of thallium and technetium scintigraphy: method for assessing within-patient interventions on infarct size

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It is established that technetium-99^{m} (^{99}Tc^{m}) phosphate compounds can be used to estimate the size of an infarct some days after its onset, and that thallium-201 (^{201}Tl) scintigraphy can show perfusion defects demonstrable early in the evolution of an infarct. ^{201}Tl imaging was performed two-and-a-half to eight (mean 5·3) hours after the onset of symptoms in 17 patients with typical history of cardiac pain >1 hour, ST elevation >5 mm, and no evidence of old infarction. ^{99}Tc^{m} polyphosphate imaging was performed in an identical left anterior oblique projection in all patients 36 to 48 hours after the onset of symptoms. The area of the ^{201}Tl-defined perfusion defect and that of the ^{99}Tc^{m} polyphosphate-defined infarct were computed after background subtraction. Clearly-defined areas both of transmural ^{201}Tl perfusion defect and Tc polyphosphate uptake were seen in 16 of the 17 patients, and these areas showed good correlation ($r=0·893$, $P<0·001$). The other patient showed a transmural defect of ^{201}Tl activity, was treated three hours after the onset of pain with glyceryl trinitrate, and subsequently showed no clearly-defined region of Tc polyphosphate uptake.

This study provides the basis of a method suitable for within-patient testing of early interventions on infarct prevention or limitation.

Exercise first pass radionuclide ventriculography in assessment of coronary artery bypass surgery

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Fourteen patients underwent exercise first pass radionuclide ventriculography (RV) before and after coronary artery bypass surgery. Twelve were angina-free on maximal exercise postoperatively and two developed angina.

In the angina-free group there was no significant change in resting left ventricular ejection fraction after surgery, but mean exercise ejection fraction rose significantly from 55·6 to 63·2 ($P < 0{\cdot}025$). Preoperatively, mean ejection fraction fell on exercise to angina from 62·8 to 56·1 per cent ($P < 0{\cdot}05$). On exercise after operation there was no change in ejection fraction compared with the resting value, which represents a significant improvement on the preoperative result ($P < 0{\cdot}05$). In the two patients who developed angina after surgery there was a mean fall in ejection fraction on exercise of 9 per cent.

Wall motion abnormalities were assessed by a hemiaxial method. In the angina-free group, all 14 zones of regional wall motion abnormalities unmasked by exercise before operation were not present postoperatively. Both regions of wall motion abnormalities induced by exercise in the patients with recurrent angina were also seen preoperatively. Coronary artery bypass graft surgery results in an improvement in regional and global ventricular function during exercise. First pass RV should prove valuable in the assessment of recurrent angina after surgery.

Vagotonic sinus bradycardia and paroxysmal atrial fibrillation

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In some patients with lone atrial fibrillation, intense bradycardia and associated atrial arrhythmias may be seen during natural periods of dominant vagal tone.

Nine patients, all male (ages 14 to 52) and free of other cardiac abnormalities gave a history of bradycardia and palpitation during sleep or relaxation. Paroxysmal sinus bradycardia (45/min or less) was seen on routine electrocardiogram or 24-hour ambulatory electocardiographic monitoring. Routine electrocardiograms were normal in all though in one P wave morphology was consistent with minor atrial conduction disturbance. Electrophysiological tests were normal in all but one patient in whom sinus node recovery was prolonged (3·5 s) only at the slowest pacing rate tested. On exercise testing there was normal sinus acceleration and prompt, often extreme, bradycardia in the immediate resting phase. Similarly, paroxysmal atrial fibrillation occurred during the rest after exercise or at other times of dominant vagal tone. Treatment with disopyramide or quinidine was successful in one of five patients, while amiodarone was effective in all three to whom it was given.

Patients with unduly pronounced effects of vagal stimulation may have paroxysmal atrial fibrillation and masquerade as sinus node disease. While pacing may help such patients symptomatically there was no evidence of organic sinuatrial disease in this series.

Do antiarrhythmic drugs depress sinus node function in patients with sick sinus syndrome?

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The potential need for pacing has been examined in 39 patients with sick sinus syndrome requiring either digoxin, propranolol, verapamil, or disopyramide for their associated tachycardias. Assessment with an acute electropharmacological pacing study for effects of these drugs on basic sinus cycle length (SCL) and on sinus node recovery time (SNRT); and with 24-hour electrocardiographic monitoring for effects of oral treatment on lowest heart rate is shown in the Table.

All four antiarrhythmic drugs depress sinus node function, though this is least pronounced with digoxin. The acute study is unreliable in predicting dangerous sinus node depression with oral treatment which should be started in hospital with temporary pacemaker cover (rate 30 bpm) and with monitoring to assess the need for permanent pacemaker implantation.

Drug	*Acute study*		*Comment*	*Chronic oral study*	
	SCL (ms)	*SNRT (ms)*		*Lowest mean HR (bpm)*	*Patients with transient bradycardia (30 bpm)*
Control	1050 ±112	1510 ±315		53 ±8	
Propranolol (n=9)	1210 ±170 (P=0·005)	2140 ±510 (P=0·001)		45 ±9 (P=0·005)	3
Control	907 ±230	1570 ±510		68·7 ±9·3	
Verapamil (n=8)	1270 ±110 (P=0·005)	1860 > 425 (P=0·005)		57·8 ±7·5 (P=0·01)	2
Control	987 ±110	1610 ±210		55 ±4	
Digoxin (n=12)	1070 ±205 (P=0·05)	1790 ±510 (P0·01)		51 ±7 (P=0·1)	1
Control	905 ±190	1740 ±310	× 1 sinus arrest > 2 min	63·7 ±11	
Disopyramide (n=10)	801 ±210 (P=0·01)	2140 ±620 (P=0·005)		59·5 ±9 (P=0·01)	4

Unexplained syncope resulting from masked sinus node dysfunction

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Electrophysiological investigation has not proved rewarding in the diagnosis of sinus node abnormalities not otherwise detected, probably because of alteration in autonomic tone induced by anxiety and by rapid atrial pacing.

Twenty-three patients with unexplained syncope or near syncope were therefore investigated by measurement of sinus node recovery time (SNRT) (2 min atrial pacing at 100 and 180/min), calculated sinus atrial conduction time (SACT), and intrinsic heart rate, before and after autonomic blockade with atropine (0·04 mg/kg) and propranolol (0·2 mg/kg). Sixteen asymptomatic controls with normal coronary arteries, haemodynamics, and conduction systems were investigated for ST-T changes only.

Intrinsic heart rate was normal in all controls but abnormal in 11 of 23 patients. SACT was normal and unaffected by autonomic blockade in both groups, as was SNRT after pacing at 100/min. SNRT was also normal before blockade after pacing at 180/min in both groups but, after blockade, though SNRT was normal in controls, it was prolonged abnormally to 158 to 325 per cent of previous sinus cycle length in nine of 23 symptomatic patients; six of these nine had a slow intrinsic heart rate, and permanent pacing relieved syncope in five. In 14 of 23 symptomatic patients with normal SNRT, only two had an abnormal intrinsic heart rate, and pacing in one did not help.

Autonomic blockade may thus increase the sensitivity of electrophysiological investigation for sinus node disorders and may unmask abnormalities of sinus node automaticity too infrequently manifest for detection by ambulatory electrocardiogram.

Spectrum of AV conduction abnormalities and tachycardias associated with anomalous Mahaim conduction

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Of 67 patients investigated for paroxysmal tachycardias associated with the WPW syndrome, six had electrophysiological evidence of anomalous nodoventricular conduction. The patients (4 female, 2 male) were aged between 13 and 58 years. All had WPW type B QRS complexes but in two patients this was intermittent. In four, regular paroxysmal tachycardias with broad QRS complexes had been documented before study. Electrophysiological studies revealed the following results: (1) short HV interval during sinus rhythm (three cases); (2) prolongation of the AH and AV intervals, with increasingly premature atrial beats in five patients. In four patients this was accompanied by increasing pre-excitation. Pre-excitation within a fixed zone of coupling intervals of premature atrial beats occurred in one patient; (3) sudden prolongation of the AH (or AV) interval at a critical coupling interval of premature atrial beats in three patients. This was accompanied by loss of pre-excitation in one patient. The sudden jump in AH was associated with an atrial echo or tachycardia in two. Atrial echo occurred in two other patients either after a sudden jump or in the absence of this phenomenon; (4) pre-excited QRS complexes during tachycardia were seen in four patients. In two of these the His spike was clearly visible with an HV interval of 0 and –25, respectively; (5) the regular tachycardias were intranodal in origin; (6) during atrial pacing, Wenckebach periods terminated by simultaneous block in both AV node and nodoventricular pathway occurred in four patients; (7) in one patient profound bradycardia in response to atrial fibrillation was noted. During this rhythm the QRS complexes were uniformly pre-excited.

The observations in this series suggest that the conduction properties of nodoventricular pathways are determined by an intimate relation of the nodoventricular pathway to the AV node and the characteristics of intranodal conduction.

Bayesian analysis of stress thallium-201 scintigraphy

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Test characteristics, true positive ratio and true negative ratio were obtained for stress thallium-201 (^{201}Tl) scintigraphy (MPI) by comparison with coronary arteriography in 100 patients. Arteriography showed significant coronary heart disease in 60 patients and normal vessels in 40 patients.

True positive ratio for MPI was 0·90 and for true negative ratio was 0·88. Using Bayesian analysis, the probability of having coronary heart disease (pCHD) for a positive MPI result and negative MPI result was calculated for prevalences of coronary heart disease ranging from 1 to 99 per cent.

Discrimination was greatest where pretest pCHD lay between 30 and 70 per cent. At pretest pCHD of 52 per cent discrimination was maximum with pCHD with positive MPI being 89 per cent and with negative MPI being 11 per cent. At pretest pCHD of 20 per cent, pCHD with positive MPI fell to 64 per cent and with a negative MPI was 3 per cent. Below 20 per cent pretest pCHD, false positive tests increased sharply. At pretest pCHD of 80 per cent, pCHD with positive MPI was 97 per cent and with negative MPI 36 per cent. Above 80 per cent pretest pCHD, false negative tests increased sharply.

These results suggest that MPI would be an inappropriate test where pCHD is low, for example, population screening, but may be useful where clinical pCHD lies between 30 and 70 per cent.

Clinical implication of normal exercise ECG and thallium-201 scintigram

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Exercise thallium-201 scintigraphy (MPI) provides a non-invasive technique for identifying the presence of coronary heart disease in patients presenting with chest pain. However, the ability of a normal study to exclude coronary heart disease is not clear. Maximal exercise testing (MET) and MPI were performed in 115 patients having diagnostic catheterisation. Image data were interpreted by computer analysis and the results compared with arteriography. In 69 patients, arteriography demonstrated significant coronary heart disease ($\geqslant 50\%$ vessel occlusion); 46 patients had normal vessels. The proportion of misclassification for normal MET, normal MPI, and combined normal MET and normal MPI was calculated.

In 46 patients with normal vessels, MET was normal in 34, MPI was normal in 39, and MET + MPI normal in 31. In 69 patients with coronary heart disease, MET was normal in 19 and MPI was normal in seven. Combined normal MET and normal MPI was not encountered in patients with coronary heart disease. The proportion of misclassification for normal MET was 36 per cent (19/53), for normal MPI was 17 per cent (7/46), and for combined normal MET and normal MPI 0 per cent (0/31). Thus, the combination of normal maximal exercise testing and normal ^{201}Tl scintigraphy occurred in 67 per cent (31/46) of patients with normal vessels and reliably excluded coronary heart disease.

What is best stress test to detect coronary artery disease using technetium-99^{m} gated cardiac blood pool scintigraphy ($^{99}Tc^{m}$ GBPS)?

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Investigations were carried out on 34 normotensive patients (15 normals, 19 coronary artery disease) with normal or only slightly impaired left ventricular function using $^{99}Tc^{m}$ GBPS at rest and during peripheral cold stimulation, isometric handgrip, and dynamic supine exercise to determine the relative potency of these interventions to provoke an abnormal left ventricular ejection fraction (LVEF) response ($>10\%$ fall) in patients with coronary artery disease. The average double product (heart rate × mean blood pressure) at rest was 7319 mmHg/min and increased with cold stimulation, isometric handgrip, and dynamic supine exercise to 11 159, 12 495, and 16 611 mmHg/min, respectively.

Patients with normal hearts had no significant change or a slight increase in LVEF with each intervention whereas patients with coronary artery disease had a significant fall in LVEF with cold stimulation ($P < 0{\cdot}001$) and dynamic supine exercise ($P < 0{\cdot}002$) but not with isometric handgrip (NS). Cold stimulation identified 15 of 19 (79%) coronary artery disease patients whereas dynamic supine exercise and isometric handgrip identified only six of 15 patients (40%) and two of 12 patients (17%), respectively. In comparison, single-lead V5 exercise electrocardiography detected only five of 19 (26%) patients with coronary artery disease.

We conclude that cold stimulation, despite evoking a smaller increment in double product, is a more convenient and sensitive stress intervention than dynamic supine exercise or isometric handgrip to detect coronary artery disease patients with $^{99}Tc^{m}$ GBPS. This may be the result of cold stimulation mediated increase in coronary vascular resistance in coronary artery disease patients not caused by dynamic supine exercise or isometric handgrip.

Comparison of thallium-201 (^{201}Tl) myocardial imaging after coronary vasodilatation with dipyridamole and after maximal treadmill exercise

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Traditional ^{201}Tl myocardial imaging is performed after maximal exercise. With many patients this is difficult because of locomotor disability, poor motivation, easy fatigue, or drug effects. Coronary vasodilatation with intravenous dipyridamole has been suggested as an alternative to exercise in demonstrating defects in myocardial perfusion.

Fifteen patients having coronary arteriography underwent ^{201}Tl imaging on two separate occasions: after intravenous dipyridamole and after exercise. Early and late images were recorded. The images were assessed independently by three experienced observers. There was good interobserver agreement, and any discrepencies were resolved by combined viewing of the images. Images were examined for diagnostic quality and for defects in activity. Myocardial/background counts were assessed by computer analysis. Correlations with the coronary arteriograms were made.

In 11 patients (73%) all images were of satisfactory diagnostic quality. In no patients were both early and late dipyridamole studies unsatisfactory. In nine patients both exercise and dipyridamole images showed defects. In five of these the late exercise image showed redistribution of activity into these defects, while redistribution after dipyridamole was demonstrated in three. In the remaining six patients there were no defects on either image.

A minor (10%) fall in blood pressure occurred after dipyridamole, and angina and ST segment depression were seen less commonly than with exercise.

Intravenous dipyridamole is a reliable alternative to exercise in ^{201}Tl imaging, and in certain patients may be the technique of choice.

Dipyridamole compared with exercise for thallium scanning

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Intravenous dipyridamole as a coronary vasodilator was compared with exercise as a method of enhancing perfusion defects for detection by thallium-201 scintiscans. Scans from 20 patients were projected individually in random order and comparisons were made only after defects had been scored by three observers. The myocardial outline was divided into two segments in PA and lateral projections and three in the LAO 45 projection. Defects were identified in 65 segments using dipyridamole and 71 segments after exercise, but only 92 of the 140 segments were scored identically as normal or abnormal by the two methods. A fair correlation was obtained when the extent of myocardial defects was quantified irrespective of site using a grid system in four projections ($r=0{\cdot}688$, $P<0{\cdot}001$). Fifteen of the series had coronary angiograms. Dipyridamole predicted the site of obstructive lesions as accurately as exercise. No important adverse effects were observed from the drug in this small series. Intravenous dipyridamole can reasonably be used instead of exercise for thallium-201 scans but there are no clear-cut advantages unless exercise testing is impracticable.

Thallium-201 myocardial imaging in triple vessel disease

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Doubts have been cast about the value of ^{201}Tl myocardial imaging because of the reported incidence of normal scans in patients with proven coronary artery disease. Our study suggests that the incidence of false negative scans is lower than previously reported.

Rest exercise ^{201}Tl imaging was performed on 70 patients who were undergoing routine coronary angiography. The scans were computer processed, code-marked, and reported from Polaroid colour photographs without knowledge of the clinical details. A perfusion defect was considered to be present where there was a discrete zone of reduced tracer activity ($\geqslant 20\%$).

Coronary angiograms were reported without knowledge of the scintigraphic findings. A vessel was considered diseased when a lesion was seen $\geqslant 70$ per cent of the vessel lumen. Of the 70 patients, 21 were found to have triple vessel disease (left main coronary lesions were taken to indicate involvement of the left anterior descending and circumflex arteries). Of the 21 patients, 20 also had technically satisfactory rest exercise scans.

Nineteen of these 20 (95%) showed exercise induced perfusion defects, so that in this study a false negative occurred in only one patient (5%). For triple vessel disease this is a higher sensitivity than previously reported, enhancing the value of ^{201}Tl imaging as a non-invasive test for coronary artery disease.

Patterns of disturbed myocardial perfusion in patients with coronary artery disease

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Fifty patients with anginal chest pain were studied to determine whether different patterns of disturbed regional myocardial perfusion with stress are useful as a physiological measure of severity of coronary artery stenoses. All the patients underwent a standardised maximum exercise test with electrocardiography, left ventricular and coronary angiography, and measurement of regional perfusion using Krypton—81m and a standardised atrial pacing test. Eleven patients with normal coronary arteries and negative exercise tests demonstrated uniform regional myocardial perfusion with pacing. In 40 of the 50 patients with significant ($\geqslant 70\%$ stenosis) coronary artery disease and positive exercise tests, atrial pacing produced both regional increases and regional decreases of myocardial perfusion. Analysis of regional perfusion in the segments showing decreases in perfusion showed three results. *Group 1:* regional perfusion in 10 patients increased significantly (by $21 \pm 7{\cdot}0\%$, $P < 0{\cdot}01$) for seven to 10 minutes of atrial pacing and then decreased to 61 ± 9 per cent below control. This group achieved 30 000 to 45 000 Joules in the exercise test.

Group 2: regional perfusion in 12 patients remained stable for four to nine minutes of atrial pacing and then decreased to $69 \pm 11{\cdot}0$ per cent ($P < 0{\cdot}01$) below control. This group achieved 26 000 to 34 000 Joules in the exercise test. *Group 3:* regional perfusion in 17 patients showed an immediate decrease in myocardial perfusion to the affected segment with the start of atrial pacing, reaching 81 ± 14 per cent below control ($P < 0{\cdot}01$). These patients achieved 7000 to 22 000 Joules in the exercise test. In all these 40 patients ST segment depression and chest pain occurred at 140 ± 17 s and 240 ± 70 s, respectively, only after regional perfusion had decreased below control values. These patients with coronary artery disease showed a close relation between the three different patterns of disturbed perfusion with stress, the workload achieved in the exercise tests, and the timing of ST segment depression. These different patterns of myocardial perfusion help our understanding of coronary stenosis.

Beta adrenergic control of coronary artery smooth muscle

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The extent to which coronary artery spasm contributes to the spectrum of coronary disease remains uncertain and there is some evidence that beta-blocking drugs may be detrimental in coronary spasm. We studied the effect of various sympathetic agonists and antagonists on the mechanical responses of isolated coronary strips from sheep hearts. The beta$_2$ agonist salbutamol exerted no effect up to 10^{-6} M, whereas the beta$_1$ and beta$_2$ agonist isoprenaline induced relaxation at 10^{-11} M. The relaxing effect of isoprenaline was competitively antagonised in a dose-related manner by the beta-blocking agents propranolol, acebutalol, practolol, and oxprenolol in concentrations of 10^{-7}, 10^{-7}, 10^{-5}, and 10^{-7} M, respectively. Though these drugs were used in approximately equipotent beta-blocking doses, the isoprenaline dose-response curves were shifted respectively ×150, ×65, ×25, and ×15, indicating that propranolol blocked the isoprenaline-induced relaxation 10 times more than oxprenolol.

This study shows that the relaxation of coronary artery smooth muscle was mediated by beta$_1$

receptors, which contrasts with beta$_2$-mediated dilatation of other vascular beds. The possession of beta$_2$-blocking properties (non-cardioselectivity) was thus irrelevant to the effect of beta-blocking drugs on coronary artery tone in these experiments. The possession of partial agonist activity appeared to minimise their antagonism of beta$_1$-mediated dilatation. These findings may be relevant to the management of coronary disease in man.

Haemodynamic effects of beta-blocking drugs in non-obstructive hypertrophic cardiomyopathy

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Beta adrenergic blocking drugs in hypertrophic cardiomyopathy provide symptomatic relief and control of atrial fibrillation but their effect on long-term prognosis is uncertain, and their acute haemodynamic effects on diastole are still unclear.

Four patients have been studied by catheter-tip manometry before and after intravenous administration of 0·05 mg/kg metoprolol. This dose did not alter average resting heart rate. Diastolic pressure volume relations were calculated from continuous pressure measurement during left ventriculography. The effect of metoprolol on end-diastolic pressure was variable, but in all patients the early diastolic pressure dip was higher after metoprolol (+5·8, $P < 0·05$) and the end-diastolic volumes were increased (+5·6, $P < 0·05$). There was an insignificant fall in the ejection fraction. Simultaneous recording of the echocardiogram, apex cardiogram, phonocardiogram/electrocardiogram before and after oral beta-blocking drugs demonstrated no consistent shortening of isovolumic relaxation time, total relaxation period, or alteration of the peak left ventricular filling rate and duration of the rapid filling phase.

Retrospective review of the clinical records of patients with hypertrophic cardiomyopathy from 1973 to 1975 showed seven patients in whom intravenous administration of practolol 0·1 mg/kg did not lower end-diastolic pressure significantly and variably affected end-diastolic volume.

It is concluded that there is insufficient evidence of improvement in the majority of patients with HOCM after beta-blocking drugs to justify their administration routinely to these patients. Specific haemodynamic or arrhythmic features which can be improved by beta-blockers must be identified in individual patients.

Effects of prostacyclin on cardiac function in man

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Prostacyclin (PGI$_2$), a potent endogenous inhibitor of platelet aggregation, has also been shown to have vasodilator activity. We have intestigated the effects of infused prostacyclin on blood pressure and cardiac function, by non-invasive methods.

Six normal male volunteers were infused with PGI$_2$ at rates of 1, 2, 4, and 8 ng/kg per min, each increment lasting 20 minutes. Before infusion and during each increment the following measurements were made: (i) blood pressure, (ii) heart rate, (iii) left ventricular echocardiographic dimensions, (iv) systolic time intervals, and (v) percentage maximum adenosine diphosphate (ADP) induced platelet aggregation.

All results refer to differences between the control period and the final increment, and are the mean value ±SEM. Diastolic blood pressure fell from 62 ± 3 mmHg to 53 ± 3 mmHg ($P < 0·02$), and heart rate rose from 62 ± 1 beat/min to 80 ± 1 beat/min ($P < 0·001$). Left ventricular end-diastolic dimensions fell from $50·2 \pm 0·31$ mm to $44·3 \pm 0·27$ mm ($P < 0·001$) and end-systolic dimensions from $30·0 \pm 0·27$ mm to $26·8 \pm 0·21$ mm ($P < 0·02$). Fractional shortening and velocity of circumfererential fibre shortening remained unchanged. The mean dose ratio of maximum ADP induced platelet aggregation was shifted to the right during PGI$_2$ at 4 (1·71; $P < 0·01$) and 8 (2·38; $P < 0·001$) ng/kg per min.

We conclude that PGI$_2$ causes a modest decline in diastolic blood pressure and increase in heart rate at rates which inhibit platelet aggregation in man. The reductions in end-diastolic and end-systolic dimensions occurring after PGI$_2$ suggest both arteriolar and venular dilatation, but there was no change in echo ejection phase indices.

Myocardial histamine type 2 receptors

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We have studied the effects of myocardial (H$_2$) receptor stimulation in man, using M-mode echocardiography to measure left ventricular dimensions. The effects of histamine infusion were compared with those of sodium nitroprusside which has no direct cardiac effects, but which, like histamine, is a potent vasodilator. Both drugs were infused at rates which caused similar falls in diastolic blood pressure, to allow for changes in left ventricular dimensions directly and reflexly attributable to vasodilatation.

A single blind, randomised, crossover study was performed in six normal men. They received 4×20 minute intravenous infusions: (i) normal saline control, (ii) mepyramine 0·05 mg/kg per min (an H_1 receptor antagonist), (iii) histamine or sodium nitroprusside to produce a 15 mmHg fall in diastolic blood pressure (mean infusion rates were 1·5 and 0·6 μg/kg per min), (iv) with histamine or sodium nitroprusside continuing, cimetidine (an H_2 receptor antagonist) in an IV bolus of 100 mg, followed by 0·2 mg/kg per min.

Mepyramine caused no significant haemodynamic effects. Plasma noradrenaline rose from 0·21 ±0·04 to 0·30 ±0·02 ng/ml after histamine, and from 0·22 ±0·03 to 0·31 ±0·07 ng/ml after sodium nitroprusside, suggesting similar activation of the baroreflex. Plasma adrenaline was not significantly increased after either drug. Heart rate increased by 12 ±4 beats/min after histamine, and 9 ±3 beats/min after sodium nitroprusside (NS).

Echo ejection phase indices did not change significantly after sodium nitroprusside, but fractional shortening and velocity of circumferential fibre shortening increased from 39·4 ±3·1 per cent and 1·30 ±0·13 s^{-1} to 55·2 ±2·1 per cent and 1·98 ±0·14 s^{-1} (P < 0·01) during histamine, returning to 40·2 ±1·2 per cent and 1·36 ±0·11 s^{-1} after cimetidine.

Myocardial H_2 receptor stimulation causes a direct positive inotropic response.

Role of alpha adrenergic stimulation in arrhythmias induced by coronary reperfusion

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In chloralose anaesthetised cats alpha receptor blockade with phentolamine or prazosin or depletion of myocardial catecholamines with 6-hydroxydopamine significantly reduced the number of premature ventricular contractions (321 ±62 *vs* 14 ±10) induced by coronary reperfusion (35 minutes after left anterior descending occlusion) and abolished mortality caused by ventricular fibrillation which occurred in 25 per cent of controls. In contrast, beta-blockade with propranolol was ineffective. Blood flow to the ischaemic zone (assessed using radiolabelled microspheres) was not affected by phentolamine before occlusion or during the hyperaemic reperfusion phase which is temporarily associated with the onset of arrhythmias. Before coronary occlusion left stellate nerve stimulation increased idioventricular rate from 66 ±6 to 144 ±7 beats/min (P < 0·01), a response that was blocked by propranolol, but not by phentolamine. In contrast during coronary reperfusion the increase in idioventricular rate induced by stellate stimulation was abolished by phentolamine (79 ±10 beats/min) but not by propranolol (203 ±14 beats/min). Infusion of an alpha receptor agonist, methoxamine (10^{-7} M) directly into the left anterior descending coronary artery via a femoral artery bypass in catacholamine depleted animals did not affect idioventricular rate before coronary occlusion but caused a significant increase (33 ±7 to 123 ±21 beats/min) during reperfusion. Thus, enhanced alpha receptor responsiveness appears to contribute to the electrophysiological derangements and arrhythmias associated with coronary reperfusion.

Heart rate responses after beta-blocker withdrawal

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Convincing evidence that a rebound beta-blocker withdrawal syndrome exists has been lacking despite anecdotal reports and general pharmacological expectation. We studied the heart rate responses in groups of euthyroid and hyperthyroid patients and normal volunteers, during and after treatment with propranolol or other beta-blockers. A significant rebound increase in heart rate occurred two to three days after stopping propranolol (160 mg/day for six weeks). The rebound appeared to depend on the degree of adrenergic activity, being exaggerated by standing, especially with vasodilatation or underlying hyperthyroidism, or combinations of these factors. The rebound phenomenon was also apparent in the heart rate responses to isoprenaline infusion or during the Valsalva manoeuvre. A similar rebound increase in heart rate occurred three to four days after stopping atenolol (200 mg/day), the recovery pattern suggesting an oscillation with periodicity of two days. Preliminary similar studies with oxprenolol (150 mg/day) showed a much smaller rebound. The findings confirm that increased adrenergic responsiveness is present after withdrawal of beta-blockers.

Dissociation between myocardial glycoside uptake and inotropic response in man

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Parenteral digitalisation is employed in left ventricular failure, though improvements do not always result and inotropic responses may lag behind plasma levels, possibly because of slow uptake.

Nine patients with left ventricular failure were studied at cardiac catheterisation using the possibly rapid-acting glycoside methyl digoxin. With consent and after stabilisation the following measurements were made before and for 30 minutes after a five-minute infusion of methyl digoxin, 11·0 μg/kg: pulmonary artery end-diastolic pressure, cardiac output, thermodilution coronary sinus blood flow, coronary sinus and arterial methyl digoxin levels by validated radioimmunoassay. In six patients left ventricular pressure and dP/dt were directly measured using catheter-tip manometers. From arteriovenous methyl digoxin difference and coronary sinus flow, quantitative myocardial uptake was derived.

In all patients within 20 minutes after infusion, coronary sinus methyl digoxin levels exceeded arterial levels, indicating that myocardial glycoside uptake had passed its peak and elution had become dominant. Peak dP/dt increased linearly from mean 1800 mmHg/s^{-1} to 2250 ($P < 0{\cdot}05$), but changes in cardiac output and filling pressure were variable and did not attain significance, possibly due to systemic resistance changes.

Rapid methyl digoxin uptake is confirmed, but is clearly dissociated from the inotropic response which itself is not translated into useful haemodynamic effects.

Autodecremental atrial pacing—microprocessor-based tachycardia termination system

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Five patients with recurrent tachycardias underwent electrophysiological studies with particular attention to termination of tachycardia by pacing techniques. These included programmed premature stimulation, overdrive, and underdrive pacing. Two patients had concealed accessory pathways involved in tachycardia and three patients had AV nodal reentrant tachycardia.

Autodecremental atrial pacing was employed in all patients. This system is controlled by a microprocessor interfaced with a stimulator and is activated automatically by heart rates of 160 beats/min or over. The initial stimulus is introduced at an interval less than the tachycardia cycle length, determined by a preset decrement (D). Each subsequent interval is reduced by D resulting in accelerated pacing for a preset period (P). The final pacing interval is limited to 218 ms. Both P and D are operator programmable variables.

In three patients, atrial extrastimuli or atrial overdrive initiated atrial fibrillation. Autodecremental pacing converted tachycardia to sinus rhythm in all cases.

The autodecremental mode avoids stimulation in the vulnerable period and gradual acceleration of pacing over a short period results in stimulation at different phases of tachycardia. These factors may reduce the risk of initiation of atrial fibrillation and provide a simple flexible means of tachycardia termination.

Evaluation of rate programmable permanent pacemakers using technetium-99m gated cardiac blood pool scintigraphy (^{99}Tc^{m} GBPS)

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The introduction of rate programmable pacemakers has recently sharpened the problem of selecting the proper rate at which to set an implantable cardiac generator. This study examines the effect of incremental right ventricular pacing on left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), and an index of the cardiac output (COI = LVEF × EDV × paced rate) measured by ^{99}Tc^{m} GBPS in seven patients using a variety of external rate-programmable pacemakers implanted long term.

In all patients at rates between 50 and 125 beats/min there was a progressive and significant fall in LVEF (17%, $P < 0{\cdot}02$) and EDV (26%, $P < 0{\cdot}005$), with a similar significant reduction of stroke volume. In contrast, COI rose significantly (27%, $P < 0{\cdot}02$).

The heart rate associated with peak COI varied from patient to patient and was not related to maximal LVEF. Peak COI was generally achieved between 95 and 103 beats/min but maximum outputs were also noted at lower ventricular rates (70/min). Prediction of optimal heart rate in terms of COI was not possible.

We conclude that: (i) incremental right ventricular pacing decreases LVEF and that little benefit is conferred by ventricular paced rates greater than 100/min.

(ii) $^{99}Tc^{m}$ GBPS is a useful technique to select the optimum paced rate in individual patients with programmable generators who need maximum cardiac output with minimal battery drain.

Modern endocardial atrial and ventricular pacing leads

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Seventy-five consecutive atrial leads (January 1977 to June 1979) and 100 consecutive ventricular leads (March 1978 to June 1979) were studied. Atrial leads were 35 passive and 40 active (screw-in) fixation types: initially there was a high displacement rate from atrial appendage, but modification to the passive type and introduction of active type have eliminated displacement. Acute atrial thresholds were 0·73 ±0·15 V at 0·5 ms. P amplitudes were 2·31 ±1·47 mV. Eight normally functioning leads were examined chronically: thresholds 1·24 ±0·26 V at 0·5 ms and P amplitudes 2·36 ± 0·73 mV. Three P wave sensing problems have developed since lead improvements (last 53 leads); all had P amplitude <2·0 mV acutely. Ventricular leads consisted of 30 to 10 mm tined, 50 to 2 mm tined, and 20 screw-in with three displacements in 10 mm tined lead which is now obsolete and only one exit block in the other 70 leads. Acute thresholds were 0·44 ±0·17 V at 0·5 ms and P amplitudes 9·01 ±4·03 mV. Four normally functioning leads were examined chronically: thresholds 1·38 ±0·55 V at 0·5 ms, P amplitudes 5·38 ±2·63 mV (minimum follow-up one month). It appears that atrial thresholds are higher acutely but rise less and are chronically comparable with ventricular. Thus advances in surgical technique of lead placement and in technology of lead design have completely eliminated displacement from both chambers with an incidence entrance/exit block of 2·5 per cent.

Surgery for ventricular tachycardia using operative pace mapping

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Simulation of ventricular tachycardia by pacing at operation (pace mapping) has been used in nine patients to indicate the site of origin of spontaneous ventricular tachycardia for surgical ablation.

All patients (seven male, two female, ages 36 to 65 years) had recurrent life-threatening ventricular tachycardia (unifocal in seven cases and multifocal in two cases) which was refractory to optimal conventional drug therapy, including amiodarone in seven cases.

The underlying diagnoses were coronary artery disease (six patients), valvular disease with coronary embolism (two patients) and cardiomyopathy (one patient).

The origin of the ventricular tachycardia was positively identified in all cases. Excision of the site implicated was undertaken in eight cases. Where multifocal arrhythmias were present only the focus judged clinically to be most troublesome was excised. In one patient the focus was judged to be surgically inaccessible for technical reasons.

Aneurysmectomy (five patients), aortocoronary bypass grafting (three patients), and valve replacement (two patients) were performed in addition to arrhythmia surgery.

After three to 25 months, five patients remain completely cured, requiring no antiarrhythmic drugs. One patient, who had multifocal arrhythmias, now requires only disopyramide to control the subsidiary foci. Two patients died of operative complications without recurrence of ventricular tachycardia and one, whose focus could not be excised, died suddenly three months after operation.

We conclude that: (1) the simple technique of pace mapping localises sites of ventricular tachycardia; (2) the nature of surgery for ventricular tachycardia is influenced by its site, and (3) the long-term results of surgery for ventricular tachycardia depend more on the extent and nature of the underlying ventricular disease than on the mapping and surgical techniques.

Computer system for high-speed analysis of electrocardiograms

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High-speed analysis of tape-recorded electrocardiograms is an important clinical and research technique. Currently available analysers perform poorly in their classification of ventricular ectopic complex pairs, ventricular tachycardia, and R on T ventricular ectopic complexes. Paper write-outs of these arrhythmias are required for corroboration but this takes more than six seconds (equivalent to six minutes on electrocardiogram) to obtain. If arrhythmias are common, and not to be missed, the tape must be stopped frequently.

Such difficulties were encountered in the analysis of electrocardiograms from 17 patients who developed primary ventricular fibrillation where 83 per cent (232/280) of all 10-second samples (with ventricular ectopic complex pairs, ventricular tachycardia, or R on T ventricular ectopic complexes) were separated by less than six minutes. A similar frequency, 86 per cent (1116/1300), was found in 21 other patients with acute myocardial infarction.

A computer analysis system has been developed to cope with these difficulties. All arrhythmias of interest are detected (both by an operator and by a Pathfinder analyser) and stored without stopping the electrocardiographic recording. Ventricular ectopic complex detector sensitivity can be increased at the expense of specificity as the electrocardiographic samples are later recalled and, if required, accepted for automatic plotting.

The computer system has improved the classification and differentiation of complex arrhythmias, reduced operator fatigue, increased accuracy, improved electrocardiograph presentation, and decreased analysis time.

Sites of origin and behaviour of arrhythmias in mitral valve prolapse: assessment using simultaneous 12 lead electrocardiography

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In 22 patients with echocardiographically confirmed mitral valve prolapse simultaneous 12 lead electrocardiograms were recorded at rest (supine) and during (a) passive head-up tilting, (b) maintained deep inspiration, and (c) graded dynamic exercise. Sites of origin of arrhythmias were determined by comparison with simultaneous 12 lead electrocardiograms obtained during electrical stimulation of various known myocardial sites in other patients during or after cardiac surgery.

Three groups of patients were identified:

(1) Eleven patients presented with chest pain or dyspnoea and had typical signs of mitral valve prolapse. Seven showed left ventricular premature beats of two distinct patterns suggesting origin in the papillary muscles. Three patients had right ventricular and two had atrial extrasystoles.

(2) Of six patients without symptoms only one had frequent right ventricular extrasystoles.

(3) Of five patients presenting with arrhythmic symptoms alone, four had frequent high right ventricular extrasystoles; one developed rapid right ventricular tachycardia on initiating exercise. One patient had second degree heart block and one showed ventricular pre-excitation.

The arrhythmias were provoked or suppressed consistently by particular manoeuvres in individual patients but showed no overall patterns of behaviour.

Thus papillary muscle arrhythmias occur commonly in symptomatic mitral valve prolapse and may have a mechanical origin, whereas right ventricular arrhythmias often occur without typical symptoms or clinical signs of mitral valve prolapse and may reflect local myocardial disease.

Echocardiographic assessment of St. Jude mitral valve prosthesis

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To assess the effects of the new bi-leaflet St. Jude prosthesis upon left ventricular filling characteristics, we determined peak rates of increase in left ventricular dimension during diastole, dD/dt, and the duration of the rapid diastolic filling period (RFP), using echocardiography in 14 patients (eight female, six male) undergoing mitral valve replacement. We compared these results with similar data obtained from 14 normal subjects and 60 patients who had had mitral valve replacement, 30 with Starr-Edwards and 30 with Björk-Shiley prostheses. All patients in this study were operated upon either for rheumatic or for degenerative mitral valve disease.

Patients	*No*	*Peak dD/dt*	*Rapid filling period*
Normals	14	16·0 ±3·2 cm/s	160 ±50 ms
St. Jude	14	13·1 ±2·6 cm/s	200 ±35 ms
Starr-Edwards	30	7·4 ±3·0 cm/s	295 ±110 ms
Biörk-Shiley	30	10·5 ±4·2 cm/s	180 ±80 ms

Peak dD/dt after mitral valve replacement with the St. Jude prosthesis was significantly greater than in patients with Starr-Edwards ($P < 0{\cdot}01$) or Björk-Shiley ($P < 0{\cdot}02$) prostheses. The duration of the rapid filling period in these patients was similar to those with the Björk-Shiley prostheses, but significantly less ($P < 0.01$) than in patients with Starr-Edwards prostheses. Septal motion returned to normal within two weeks in 50 per cent of patients with the St. Jude valve, whereas this was rare with Starr-Edwards and Björk-Shiley valves, only occurring with paravalvular regurgitation. In conclusion, the effects of the St. Jude valve on left ventricular filling assessed echocardiographically indicate that it approximates closely to normal and is less obstructive than either the Starr-Edwards or the Björk-Shiley prosthesis in the mitral position.

Long-term clinical and haemodynamic follow-up of patients with mitral valve repair

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One hundred and thirteen hospital survivors with mitral valve repair have been followed up from three to 19 years. Early in the series patients with commissural adhesion, light calcification, and mild mixed disease were accepted for mitral valve repair. Actuarially 82·4 ± 12·1 per cent and 65·1 ± 18·1 per cent of all patients are expected to be alive 10 and 19 years after operation, respectively. Bacterial endocarditis occurred in three (2·6%) patients. The onset of bacterial endocarditis was early in two and late in one patient. None of the patients in this series received anticoagulant treatment. Systemic embolisation occurred in six (5·3%) patients (0·61 episodes for 100 patient years). The emboli were early in three and late in the other three patients. Twenty-six (23·0%) patients underwent reoperation one to 183 months (mean 77·6 ± 11·1) after mitral annuloplasty. Early clinical deterioration (caused by dehiscence of annuloplasty in three and endocarditis in two patients) led to reoperation in five patients (19·2%) while the progression of mitral valve disease was responsible for reoperation in 21 patients (80·8%); 90·1 ± 5·9 per cent of patients are predicted to be free from reoperation five years after operation, while at 10 and 15 years the figures are 77·2 ± 13·9 per cent and 53·8 ± 23·9 per cent, respectively.

Postoperative haemodynamic investigations performed in 18 patients at a mean duration of eight-and-a-half years (range four to 11) showed significant reduction in both mean pulmonary artery and wedge pressure as compared with preoperative values. The mean diastolic gradient across the mitral valve was 10 ± 2·0 mmHg at rest and 24 ± 3·0 mmHg during exercise; 84 per cent of the patients were in grade III and IV (NYHA) preoperatively while 92 per cent of patients were in grade I and II at the latest postoperative evaluation.

Mitral valve repair provides satisfactory long-term clinical and haemodynamic improvement in a selected group of patients and should always be considered in the management of mitral regurgitation. When deterioration occurs this is usually a result of the progression of mitral valve disease.

Mitral valve replacement without long-term anticoagulants (8·5 years' experience with periocardial xenograft)

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Mitral valve replacement was undertaken in 236 patients (180 single and 56 multiple) with pericardial xenografts. There were 7·6 per cent early and 5·1 per cent late deaths and none was valve related. Between 1971 and 1976 no anticoagulants were used at any time (group 1, 67 patients). Since 1976, all patients received warfarin for the first four to six weeks after operation (group 2, 113 single, 56 multiple); 70 per cent of all patients were in chronic atrial fibrillation. One patient from group 2 and four from group 1 had mild and transient pareses at two, three, 17, 30, and 42 days after operation, respectively. None of the patients with single mitral valve replacement, from group 2, had embolic episodes. Valve thrombosis and late embolisation have not been encountered in the entire series. The incidence of embolism was 1·02 episodes per 100 patient years (0·93 for single and 1·69 for multiple). Actuarially 97·1 ± 1·4 per cent of all patients are expected to be free from embolism at one and nine years after operation. The ratio of early embolism between group 1 and group 2 was 10:1.

The published data for mitral replacement with porcine xenografts show a higher embolic rate (3·8 to 5·3 episodes per 100 patient years) with a significant number of patients on long-term anticoagulants.

The lack of valve thrombosis and the very low embolic rate in mitral valve replacement with pericardial xenografts without long-term anticoagulants is a result of the superior hydraulic characteristics of this valve. Short-term postoperative anticoagulation is beneficial for patients with mitral and multiple valve replacement.

Cross-sectional echocardiographic recognition of vegetative endocarditis

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The cross-sectional echocardiographic (CSE) findings in 19 patients thought diagnostic of vegetations of endocarditis were reviewed in order to characterise their appearance and to determine their specificity. Of the 19 patients with cross-sectional echocardiographic features of vegetations, 13 had proven endocarditis diagnosed on strong clinical evidence in five (three aortic, one mitral, one both valves) with surgical confirmation in the remaining eight (all aortic). Six patients were incorrectly diagnosed as having vegetations (one aortic homograft, five mitral). The cross-sectional echardiographic appearance of aortic valve vegetations (12 patients) were of dense homogeneous echo masses in 10 patients, with evidence of diastolic prolapse into left ventricular outflow tract in six. All patients with prolapsing vegetations underwent early aortic valve replacement. Two patients had non-homogeneous atrioventricular echo masses which prolapsed and at operation had cusp rupture with healed vegetations. Mitral valve vegetations observed in two patients were dense and homogeneous and prolapsed through the mitral valve in diastole in both cases. Of the six patients incorrectly diagnosed as having vegetations, the appearances were less characteristic, being less dense and less homogeneous in all six cases. One patient had a leaking atrioventricular homograft with cusp degeneration and prolapse at surgery. Of the remaining five patients, two had previously treated endocarditis and presumably healed vegetations, two patients had angiographic mitral valve prolapse only, and one patient had suspected rupture of mitral valve chordae.

Cross-sectional echocardiography is valuable in confirming the presence of vegetations when they are dense homogeneous and prolapse into the left ventricular outflow tract from the atrioventricular position. Using less characteristic criteria, particularly when defining mitral valve vegetations, may lead to errors in diagnosis.

Estimation of cardiac output by echocardiography using left atrial dimensions

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Cardiac output has been estimated at echocardiography using two assumptions:

(1) The rate of increase of left atrial volume during ventricular systole is representative of pulmonary venous flow throughout the cardiac cycle.

(2) Left atrial volume (LAV) is given by: $\mathrm{LAV} = 7{\cdot}0/(2{\cdot}4+\mathrm{D}) \times \mathrm{D}^3$, where D = LA dimension (in cm) measured from the posterior aortic wall to the LA posterior wall.

Cardiac output was then calculated as:

$= ((^{\mathrm{LAV}}\text{late ventricular systole} - {}^{\mathrm{LAV}}\text{early ventricular systole}) \times 60)/\text{Time interval between LA dimension measurements (s)}$

Ten cardiac cycles were analysed and the means taken.

The validity of the technique was assessed by comparison with dye dilution measurement of cardiac output in 22 consecutive patients after cardiac catheterisation. Thirteen had valvular disease, seven had coronary heart disease, one had cardiomyopathy, and one was normal. Cases with mitral reflux or shunts were excluded.

Mean cardiac output by dye dilution was 3·92 (SD 1·24) l/min (range 1·8 to 6·6): by echocardiography the mean was 3·80 (SD 1·11) l/min. The correlation coefficient was 0·92.

The left atrial echocardiographic dimension used is more easily obtained than simultaneous echoes of the left ventricular walls, and, unlike cardiac output estimation from left ventricular volumes, the calculation appears not to be affected by left ventricular dysynergy or aortic reflux.

Cross-sectional and M-mode echocardiography in acute aortic dissection

A A McLeod, M J Monaghan, P J Richardson, G Jackson, D E Jewitt
King's College Hospital, Denmark Hill, London

Eighteen patients who suffered thoracic aortic dissections were studied using cross-sectional and M-mode echocardiography. The echocardiogram was recorded and interpreted before angiography.

Recordings were considered highly suggestive of dissection involving the ascending aorta if they showed a dilated and abnormal aortic root together with evidence of either pericardial effusion or aortic regurgitation.

Fifteen patients suffered DeBakey type I or type II dissections. The echocardiogram was positive by the above criteria in 13 of these. Cross-sectional echocardiography enhanced the imaging of aortic root anatomy and also allowed visualisation of an intimal flap. In addition, a new diagnostic feature was observed on M-mode recordings in five patients. This consists of a bizarre low-frequency movement of the aortic cusps during systole. Left ventriculography suggests that this results from interruption of the cusp attachments of the valve.

In the remaining three patients, a DeBakey type III dissection was present. Only one of these was detected. Cross-sectional echocardiography performed from the suprasternal notch was used in this case.

This study suggests that the sensitivity of echocardiography in detecting aortic dissection may be higher than previously described. The inclusion of a new echocardiographic criterion enhances the sensitivity of the M-mode technique.

Aortocoronary bypass surgery for prophylaxis only: what is the size of the problem?

Raphael Balcon, Martin Cattell, George Feurelicht
London Chest Hospital and Cardiothoracic Institute, Bonner Road, London

Retrospective and prospective data suggest that certain patients with coronary artery disease benefit prophylactically from surgery. An oversimplified definition of the extent of the disease has been used. We have defined disease strictly, selecting patients with coronary indices $\leqslant 25$ per cent including all with major proximal stenoses of the three main coronary trunks and left main stenosis. Of 416 such patients, 158 were treated medically and 258 surgically. The difference in survival at one year is 19 per cent, at two years 33 per cent, and at three years 43 per cent, and is similar for normal or abnormal ventricles. It is therefore important to select these patients for operation. They are drawn from over 3000 patients with known or suspected coronary disease who underwent coronary arteriography; 77 per cent had grade 2 angina or worse and only 9 per cent were asymptomatic, 88 per cent had a maximum exercise performance of $\leqslant 600$ kpm including 87 per cent of the asymptomatic or grade 1 angina patients.

These data suggest that the majority of patients likely to benefit prophylactically from surgery will also have symptoms that warrant its consideration; most of the small number of patients who do not could be selected by exercise testing. The often-stated problem that investigation centres would be unable to cope with the large numbers of coronary arteriograms necessary to select the relatively small number of patients may not, in fact, exist.

Coronary surgery after recurrent myocardial infarction: progress of trial comparing surgical with conservative management for asymptomatic patients with advanced coronary disease

R M Norris, P W T Brandt, A R Kerr,
A H G Roche, B G Barratt-Boyes
Green Lane Hospital, Auckland, New Zealand

A randomised trial of surgical versus conservative treatment has been carried out for male patients up to 60 years of age who have recovered from a recurrent myocardial infarct. Of 205 cases considered, 100 were relatively asymptomatic and had coronary anatomy favourable for bypass grafting; these patients fulfilled the trial conditions and were randomised (50 surgical, 50 medical). In 40 cases (elective medical group) randomisation for surgery was not considered justifiable because of relatively unfavourable coronary anatomy and/or severe left ventricular dysfunction. Twenty patients had elective surgery because of disabling angina despite full medical treatment or for significant left main coronary stenosis. In 45 cases investigation of coronary anatomy was not undertaken because of medical contraindication or patient reluctance to enter the study.

Actuarial survival curves (mean follow-up 3·5 years) show an annual mortality rate of 3 to 4 per cent per year for all investigated patients, and no advantage for any treatment group. Results suggest that in the absence of disabling angina or left main coronary stenosis, coronary artery surgery need not be advised for survivors of recurrent infarction who have severe coronary artery disease. Moreover, the prognosis for this group of patients with conservative treatment appears to be better than has been previously described.

Anomalous origin of left coronary artery from anterior aortic sinus: potential cause of sudden death—anatomical characterisation and surgical treatment

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I Mustafa
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Acadamisch Ziekenhuis, Wilhelmina Gasthuis,
Amsterdam

Three patients with the syndrome of anomalous origin of the left coronary artery from the anterior aortic sinus presented at the ages of 14, 30, and 33 years, respectively, with angina of effort. There were associated electrocardiographic changes in two. One patient had additional aortic regurgitation. Coronary angiography showed characteristic appearances of the anomaly. Two patients were treated surgically. The left coronary artery arose from the anterior sinus in very close relation to the intercoronary commissure and passed deep to that commissure in the substance of the aortic wall for a distance of approximately 1 cm before following its normal course. Correction of the anomaly was achieved in one patient by temporary detachment of the commissure, and deroofing the left coronary artery to the mid-point of the left coronary sinus and by homograft replacement of the aortic valve and root with anastomosis of the left coronary artery to the coronary orifice of the homograft in the second. Both patients are symptom-free, with no evidence of perioperative or late myocardial infarction 12 and 24 months after operation. Repeat exercise test and coronary angiography in the younger patient have shown normal findings.

Late results of resection of left ventricular aneurysm

M Halim, I Mustafa, M Towers, M Yacoub
Harefield Hospital, Middlesex

Between August 1969 and July 1979, 111 patients underwent resection of left ventricular aneurysm. Of these, 49 were operated on before July 1974, thus giving a minimum follow-up period of five years. There were 42 men and seven women, ranging in age between 28 and 65 years (mean 52·6). The presenting symptom was angina in 10 (20%), dyspnoea in 23 (46%), and both in 12 (24%). Arrhythmia was present in six. Pre-existing systemic hypertension was present in four. Additional coronary grafting was performed in 27 patients (55%). There were four (8%) early and 15 (31%) late deaths (mean follow-up 59·8 months). Actuarial survival was 81·8 per cent at three years, 69·6 per cent at five years, and 61·3 per cent at seven years. The cause of late death was cardiac in 12 (80%), other conditions in two (13%), and unknown in one (7%). Late survival was 90 per cent for patients presenting with angina, 70 per cent for those with shortness of breath, and 25 per cent for those presenting with both. There were no early or late deaths in patients operated on for arrhythmia. Of the surviving patients 83 per cent were symptom-free or improved, and 17 per cent the same or worse.

It is concluded that the late results of resection of left ventricular aneurysm are probably better than the natural history of this condition and are related to the presenting symptoms.

Incidence and significance of late myocardial infarction after coronary artery bypass grafting

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Between October 1969 and May 1979, 978 patients underwent coronary artery bypass grafting (CABG) at Harefield Hospital. Of these, 783 had isolated CABG and 2112 grafts were inserted (2·6 grafts per patient). Late myocardial infarction, as diagnosed by clinical, enzymatic, or electrocardiographic criteria, was diagnosed in 34 (4·3%) of the surviving patients (mean follow-up of 40·5 months). There were 20 anterior and 14 inferior infarcts. Infarction occurred in the territory of grafted vessels in 28 (82%), while in six patients (18%) it was in the area of a non-grafted vessel. There were eight deaths (22%) of which five occurred within four weeks of infarction. Twenty-six patients survived infarction and were followed up for a period of two to 70 months (mean 26·6); 18 (69%) had recurrence of symptoms. Twenty-one patients were reinvestigated by repeat angiography. The patency rate of grafts to infarcted areas was 47 per cent. Left ventricular segmental wall motion showed deterioration in 14 out of 18 (78%) and was unchanged in four (28%).

It is concluded that late myocardial infarction after CABG is uncommon, carries a bad prognosis in terms of symptomatic outcome and left ventricular segmental wall motion analysis, and is related to progression of disease in approximately 50 per cent.

Atrial and ventricular human myosin during development

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Hospital

Myosin, the major contractile protein of the myofibril was prepared from human myocardium excised soon after death. The low molecular weight light chain subunits involved in actin-binding and actomyosin ATP-ase activity were examined using two-dimensional polyacrylamide gel electrophoresis. The rate of ATP-ase activity determines the contractile speed of the muscle, and abnormal activities have been observed in various pathological conditions, for example hypertrophy and cardiac failure. Myosin from the free right and left adult ventricle wall was identical with two light chains, VLC-1 and VLC-2 of molecular weight 25 900 and 18 000, respectively. Adult right and left atrial myosin light chains (ALC-1 and ALC-2) were different electrophoretically from adult VLC-1 and VLC-2. Adult atrial myosin possessed a Ca^{2+} ATP-ase activity double that of ventricular myosin. Myosin from the right and left ventricle of 18 to 21-week human fetuses contained not only adult type VLC-1 and VLC-2 but significant amounts of ALC-1. Similar amounts of ALC-1 were present at 34 weeks but only small amounts were present eight months after birth. The presence of different myosins with varying activities in the normal myocardium during development may be the basis of similar changes in activity observed in the hypertrophied heart.

Morphology and fibre orientation of human left ventricle

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Models of cardiac function which assume the left ventricle to be homogeneous and isotropic have been proposed on the basis of both pressure and volume measurements and experiments on isolated cardiac muscle. It would be more appropriate to base such models on knowledge of the morphology of the human left ventricle. To provide this information we studied the anatomy and fibre orientation in 10 human hearts from patients without clinical evidence of cardiovascular disease. Left ventricular fibres can be traced from the mitral annulus, aortic and pulmonary roots. They pass either longitudinally to the apex and thence deeply to enter the septum or more obliquely around the left ventricular free wall to enter the right ventricle. Reflection of the outer fibres reveals a middle layer arranged more perpendicularly to the long axis. Deep to this is a third layer at about 90 degrees to the outermost layer. These divisions into layers illustrate the general disposition of fibres. There are important regional variations. The septum is largely composed of fibres from the middle layer of the left ventricle. Around the mitral orifice the arrangement is circular while it is longitudinal at the apex. Fibre orientation in man thus differs significantly from that previously described in other species, and is likely to be a major determinant of normal and abnormal left ventricular wall mechanics.

Immunofluorescent studies of sera and cardiac muscle from patients with cardiomyopathy

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East Birmingham Hospital

Although there is controversy concerning the presence of circulating heart antibodies in patients with primary cardiomyopathies, the present consensus is that they are not present to any significant extent. However, Das *et al.*[1] have suggested that this lack of circulating antibody may be a result of its binding to cardiac muscle.

We have simultaneously obtained sera and left or right ventricular biopsies from 31 patients undergoing diagnostic cardiac catheterisation. Eight of these had primary cardiomyopathy, five hypertrophic cardiomyopathy, three alcoholic cardiomyopathy, and three myocarditis. The remainder were found to have other significant cardiac lesions.

Cardiac muscle and sera were examined by two independent observers unaware of the final clinical diagnosis. Using the direct immunofluorescent technique, biopsies were examined for the presence of bound IgG, IgA, IgM, fibrin, and complement. An indirect immunofluorescent method using baboon heart and the patient's own biopsy as substrates was used to detect circulating heart antibodies.

There was no correlation between the presence or absence of weakly reacting serum antibodies and the variations in intensity of direct fluorescence seen between biopsies.

We conclude that there is no evidence that the lack of circulating heart antibodies in patients with cardiomyopathy is a result of the binding of these antibodies to cardiac muscle. These results are further evidence against a primary role of humoral antibodies in the pathogenesis of primary cardiomyopathies.

Reference

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Diagnostic and prognostic aspects of endomyocardial biopsies

E G J Olsen, U Baandrup, R A Florio,
P J Richardson
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Morphological evaluation of endomyocardial biopsies has been undertaken by semiquantitative and quantitative measurements in 361 biopsies from 201 patients suspected to suffer from cardiomyopathy. The findings have been related to clinical and haemodynamic indices such as length of history, ejection fraction, and left ventricular end-diastolic pressure.

At light microscopical level pooling of quantitative results shows characteristic features of some entities, and grouping of patients is marginally more accurate than that achieved by conventional histological examination. Normal tissue can be separated from pathological samples, but sufficient basis for a definite distinction between individual patients with abnormal histology has not been established. Furthermore, no correlation between quantitative morphology and clinical or haemodynamic information has been found.

A group of 48 patients has been analysed semiquantitatively at electron microscopical level. No relation with haemodynamic measurements or assessment of prognosis can be established.

Analysing endomyocardial biopsies from hearts at necropsy it has been found that five biopsies at least are required to reflect accurately the state of the myocardium.

It is concluded that endomyocardial biopsy plays an important role as an adjunct to diagnosis, that morphometry increases accuracy of the findings, but that prognostic evaluation should be interpreted with the greatest caution.

Abnormal electrocardiograms in athletes

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Departments of Cardiology, Northern General Hospital, Sheffield, and Royal Postgraduate Medical School, London

Nine athletes aged between 18 and 41 had electrocardiograms recorded during routine examinations. The electrocardiograms were regarded as abnormal, six on account of left ventricular hypertrophy with T wave changes, one because of anterior Q waves, and two because of T wave changes only. All the athletes had been advised to relinquish their sporting activities and ambitions but had been referred for a further opinion.

The referral diagnoses were cardiomyopathy (in three), hypertrophic cardiomyopathy (in two), ischaemic heart disease (in two), and uncertain (in two).

Each patient had a full examination, rest and exercise electrocardiogram, chest *x*-ray, echocardiogram, and cardiac catheterisation. Coronary arteriograms were performed in seven.

No patient was hypertensive. Soft third sounds, fourth sounds (palpable in three), and systolic murmurs were common. The chest *x*-ray was normal in all. The echocardiogram was normal in five, showed symmetrical hypertrophy in two, and asymmetrical septal thickening in two. The left ventricular angiograms were thought to show hypertrophy in three, but only one was definitely abnormal. This showed discrete anterior wall dyskinesia: four of the exercise tests resulted in normalisation of the T wave changes. All coronary arteries appeared widely patent (including the arteries of the patient with the abnormal angiogram). Eight of these patients were considered to have normal hearts and were advised to resume their training. One was thought to have suffered a traumatic infarct. Two patients had insurance loading withdrawn and one regained his civil pilot's licence.

Harm may be done if the probable normality of 'abnormal' electrocardiographic abnormalities in athletes is not recognised. Though normalisation of T wave changes on exercise and a normal echocardiogram help to exclude significant pathology, invasive studies are fully justified when the possibility of heart disease threatens to disrupt the patient's life.

Correspondence

Br Heart J 1980; **43:** 124

Complications of pulmonary vein angiography

Sir,
I read with interest the paper by Alpert and Culham[1] and the letter by Singh and Astley[2] published in *Br Heart J*, **41:** 727–9; 740. Alpert and Culham[1] reported extravasation of contrast material into a bronchus causing severe bronchoconstriction after a pulmonary vein angiogram. They suggested that it may be possible to avoid this complication by the use of an end-hole balloon catheter in wedge position, slow flow rates of contrast material, and low-pressure injection. Singh and Astley[2], commenting on this paper, have recommended a less wedged position of the catheter tip and a preliminary hand injection to check the suitability of the catheter position as well as withdrawal of the catheter immediately after the completion of the injection. We[3] have injected 0·3 ml/kg body weight of contrast material via an end-hole catheter in a wedge position but have distributed the calculated contrast material over a two-second period so that the contrast could be delivered under low pressure (less than 100 psi). We have also suggested that the catheter be withdrawn into the left atrium immediately after injection. Since the publication of our report,[3] we have performed pulmonary vein wedge angiography in six additional patients using the same technique. In each patient there was excellent visualisation of the ipsilateral pulmonary arteries, with no complications. Based on this we agree with slow flow rates and low-pressure injection,[1] but we suggest the use of a conventional end-hole catheter in the wedge position. Our concern about the injection of large quantities of contrast material under high pressure into the pulmonary vein as suggested by Singh and associates[4] is reinforced by the complication reported by Alpert and Culham.[1]

On the basis of our experience, we will continue to recommend pulmonary vein wedge angiography for demonstrating pulmonary arteries when they cannot be visualised by conventional anterograde techniques. An injection of 0·3 ml/kg of contrast material, over a two-second period, under 100 psi of pressure, appears to be a safe and adequate amount for pulmonary vein wedge angiography.

P Syamasundar Rao,
Department of Pediatrics,
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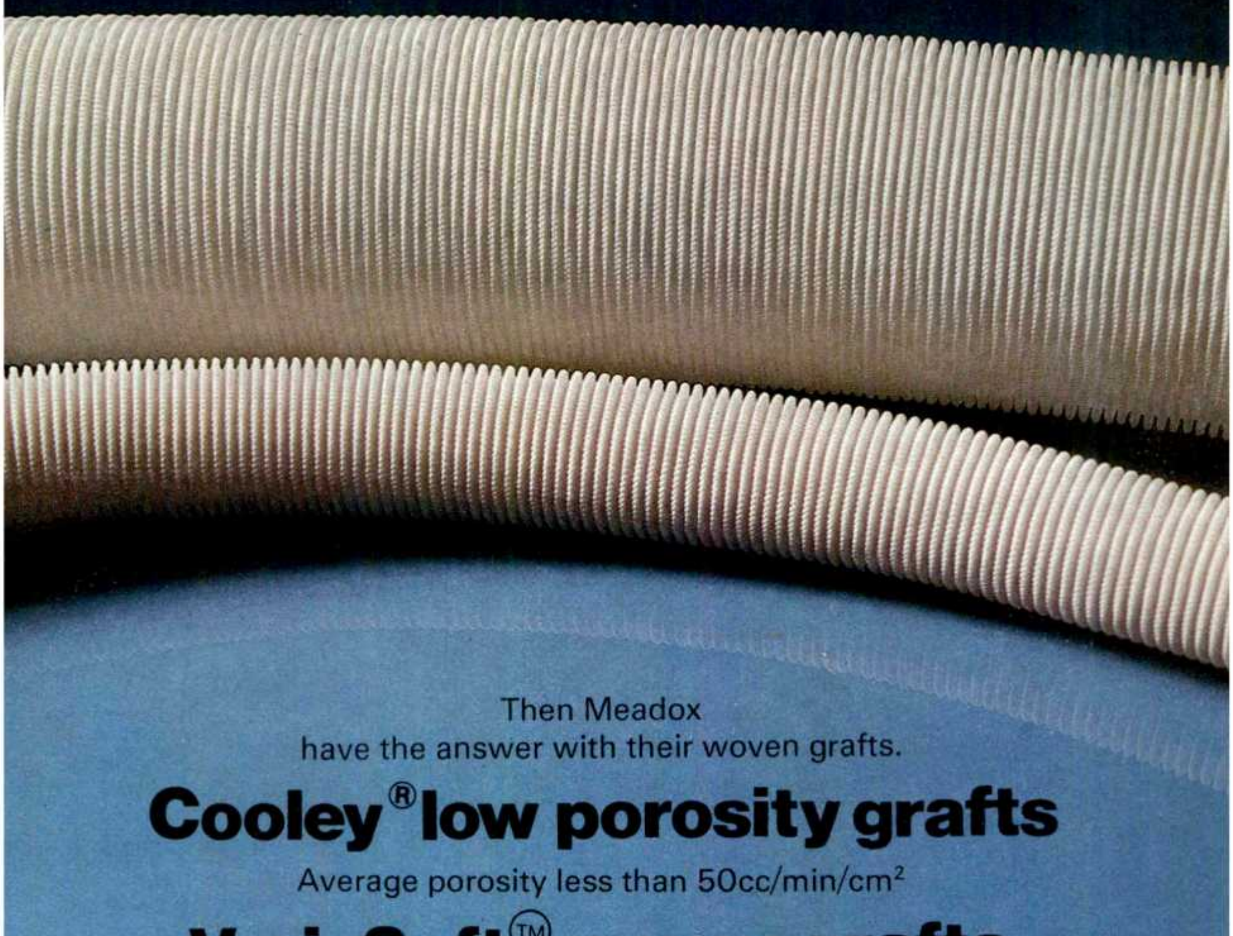

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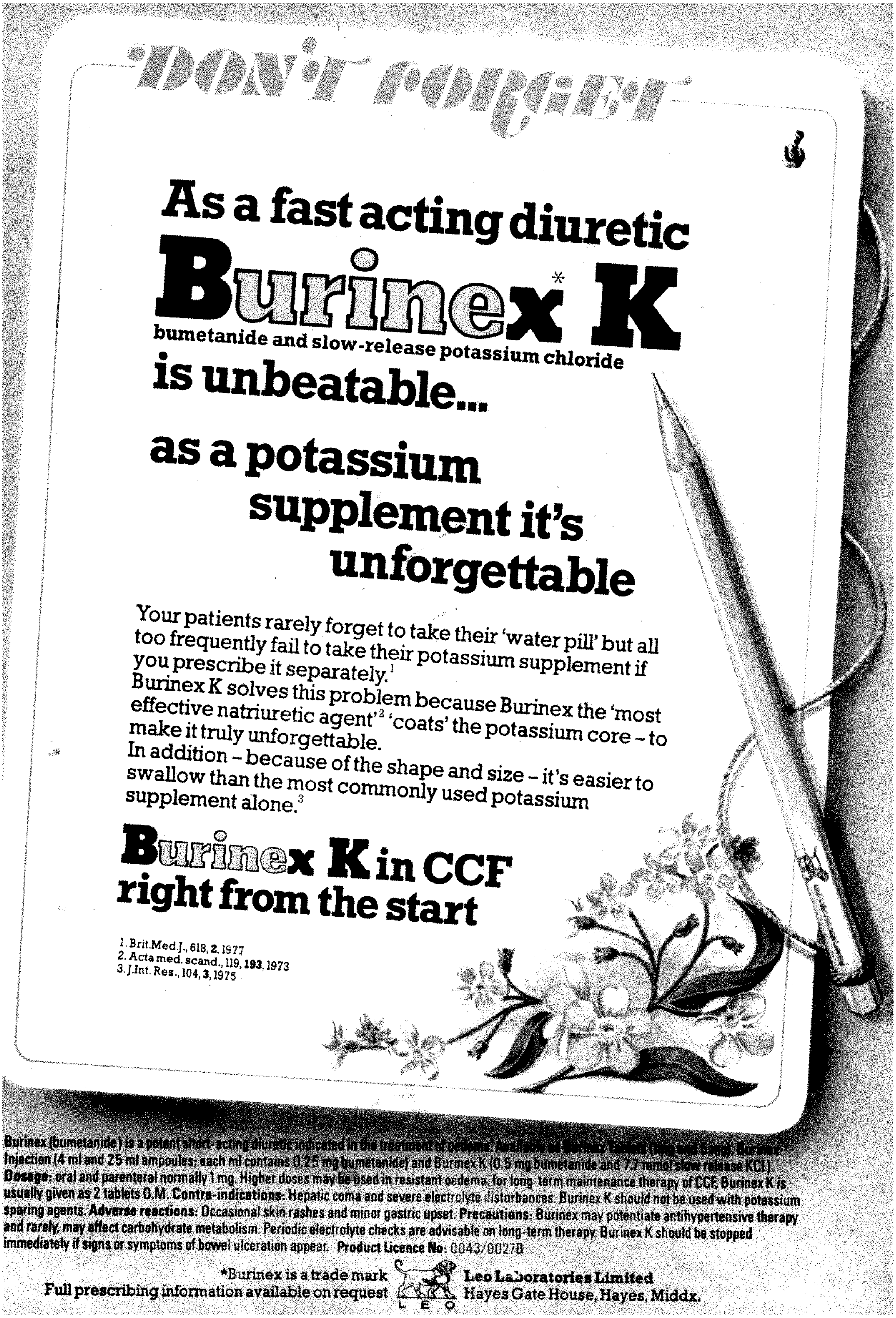

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41:** 263–67.

(2) *Books and other monographs:*
Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology* 1977. Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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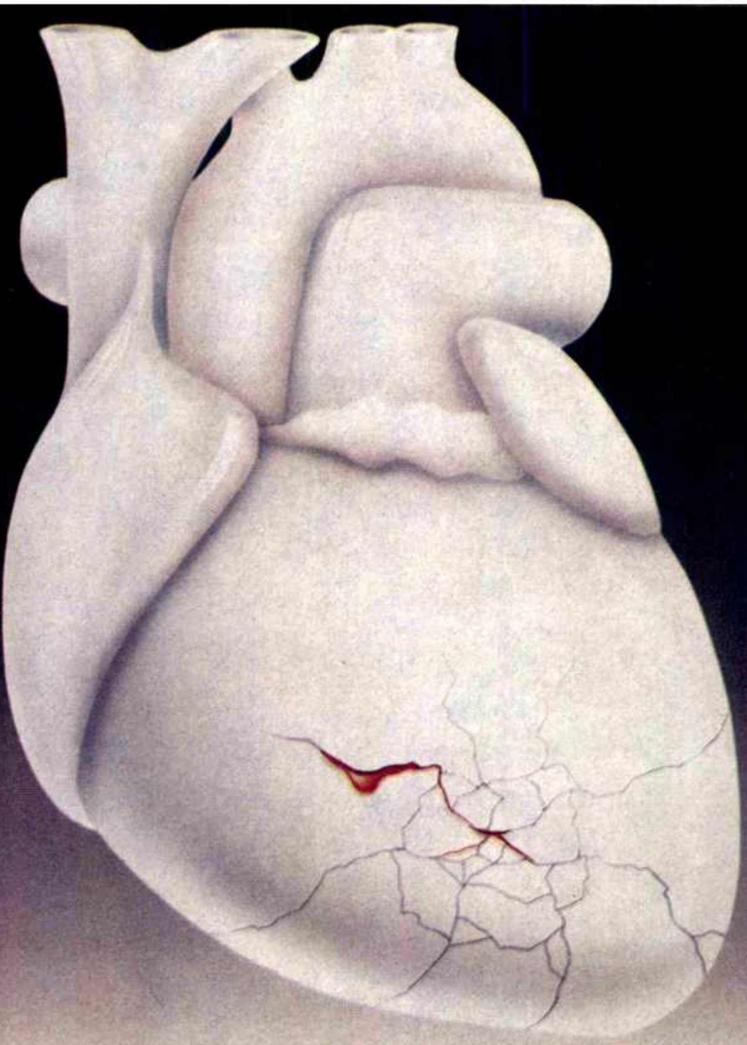

Is sudden death inevitable?

Unsuspected coronary artery disease results in sudden death in as many as 20% of cases[1] Since the majority of these fatalities are due to ischaemic heart disease (IHD),[2] effective prophylactic measures for those at risk – patients with persistent anginal pain, cardiac arrhythmias, and complicating factors such as hypertension – are of the utmost necessity.

SOTACOR is unique among the ß-blockers since it is the only ß-blocker available that has both class II and III anti-arrhythmic activity; SOTACOR provides cardio-protection in angina patients[3,4] and prevents the establishment of ventricular ectopic beats[5]

Recent clinical work[5] demonstrates an 88.5% reduction in ventricular ectopic beat frequency in patients with ischaemic heart disease receiving SOTACOR.

SOTACOR achieves 24-hour ß-blockade[6] from a single daily dose, so affording protection for patients with angina or arrhythmias – protection against excessive sympathetic stimulation and against rapid repolarisation of the myocardium.

A recent clinical study concluded:

"...in situations where ventricular anti-arrhythmic therapy is deemed necessary, especially if long-term use is considered, sotalol seems to be the agent of choice."[5]

SOTACOR*

Sotalol hydrochloride

Preserves myocardial integrity in IHD

PRESCRIBING INFORMATION Product Licence Numbers 80mg tablets 0125/0076, 160mg tablets 0125/0093. **Dosage** *1. Hypertension:* Initial daily dose should be one 160mg tablet. The majority of mild to moderate hypertensives will respond to one tablet daily and be adequately controlled at this level. *2. Angina Pectoris:* Initial daily dose should be one 160mg tablet. The majority of anginal patients will be controlled at this dosage level. N.B. – A gradual transfer of therapy over a two-week period is recommended in patients receiving other anti-anginal therapy. *3. Arrhythmia:* In the management of cardiac arrhythmias, as prophylaxis or maintenance therapy, Sotacor dosage will normally be between 160mg and 240mg daily. *Sotacor is not intended for administration to children.* **Side-effects** Minor side-effects such as bradycardia, nausea, insomnia, lassitude and diarrhoea have been reported. There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. *Cessation of therapy should be gradual.* **Precautions** Sotacor should not be used where there metabolic acidosis; history of bronchospasm; diabetic keto-acidosis. Beta-blockade may precipitate heart failure in subjects with poor cardiac reserve or may aggravate existing heart failure. Patients whose heart failure is well controlled with digitalis and diuretics may be given Sotacor. It is unnecessary to discontinue Sotacor prior to most forms of elective surgery. Caution is advised however in use of some anaesthetics in patients receiving Sotacor. **Basic NHS Price** Sotacor 80mg 100 tablets £6.52; Sotacor 160mg Compliance pack of 56 tablets £5.87.

References 1. Kannel, W.B., Doyle, J.T., McNamara, *P.M. et al. Circulation* 1975; 51(4): 606-613. **2.** Lown, B. *Am J. Cardiol* 1979; 43(2): 313-328. **3.** Gooding, P.G., and Berman, E. *Postgrad Med J.* 1974; 50: 734-736. **4.** Lima, A.B., Giannini, S.D., Scatolini, W. *et al.* Advances in beta-adrenergic blocking therapy – solatol. Amsterdam: *Excerpta Medica,* 1974; II: 65-70. **5.** Myburgh, D.P., Goldman, A.P., Cartoon, J. and Schamroth, *J.M. S. Afr Med J.* 1979; 56(8): 295-298. **6.** Lehtonen, A. and Sundquist, H., *Curr Ther Res* 1978; 23(2 Section 1): 131-135.

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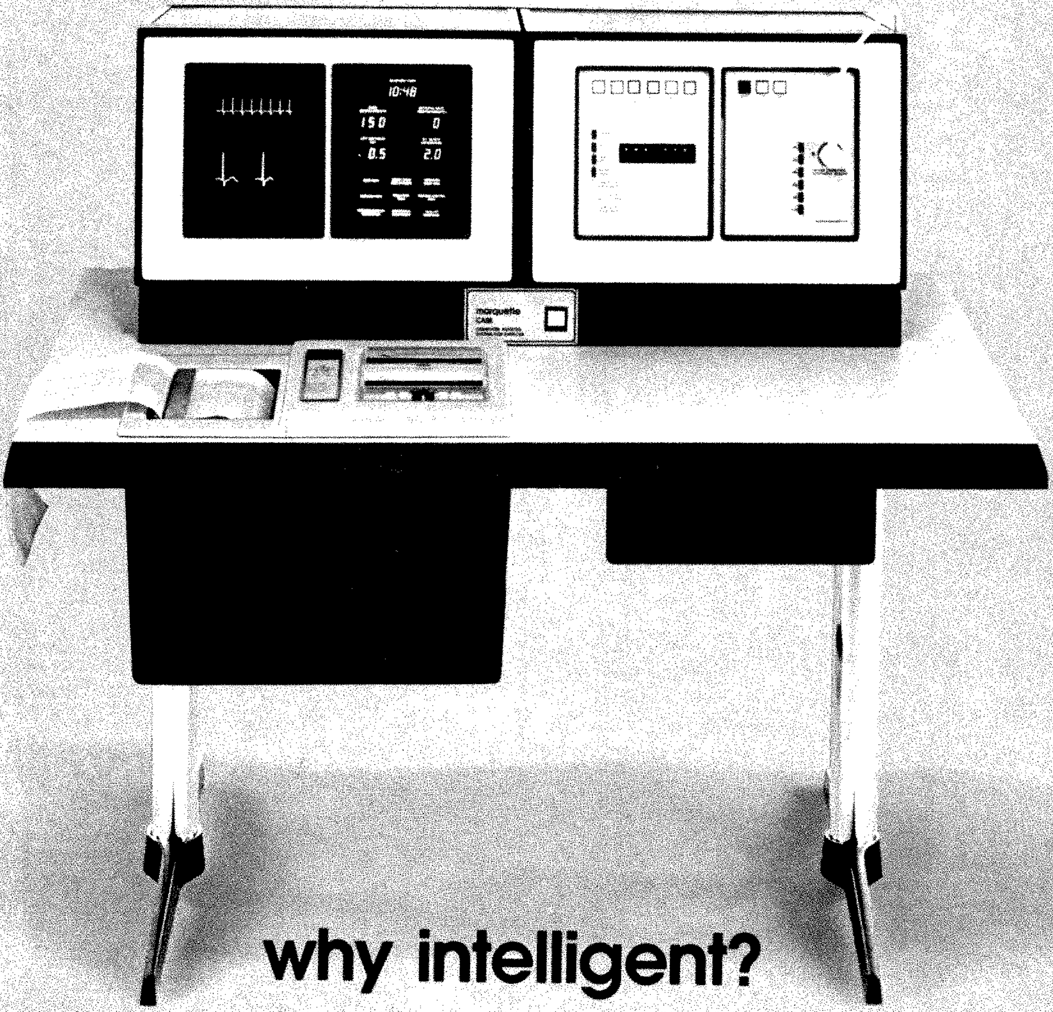

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The once daily treatment

Prescribing Notes:
Presentation Slow-Trasicor tablets each contain 160mg oxprenolol hydrochloride BP in a special sustained-release formulation available in simple daily reminder packs of 28 tablets. **Dosage in hypertension** Initially one or two tablets in the morning. **Dosage in angina** Initially one or two tablets in the morning. An evening dose may be beneficial in nocturnal angina. As with other beta-blocking drugs, sudden withdrawal of treatment may induce severe and continuous angina. Patients should, therefore, be advised to avoid interruption of established therapy and if withdrawal becomes necessary it should be done gradually. **Side effects** Dizziness, drowsiness, headache, insomnia, excitement and gastro-intestinal disturbance may occur and, rarely, isolated cases of excessive bradycardia. Beta-blockers are occasionally associated with skin rashes and/or dry eyes. If any such reaction is suspected, treatment should be withdrawn gradually. **Precautions** If there is evidence of cardiac failure this must be controlled by digitalis and/or diuretics before and during Slow-Trasicor therapy. Should the pulse rate fall below 50 per minute, then treatment should be restarted at a lower dose. Caution should be observed when treating asthmatics, chronic bronchitics or other individuals where bronchospasm may be provoked. Slow-Trasicor should be given cautiously to patients with alcoholism, metabolic acidosis, during pregnancy or anaesthesia with ether or chloroform. Beta-blockers can mask symptoms of hypoglycaemia and also affect carbohydrate metabolism. It may therefore be necessary to readjust the insulin requirements in diabetic patients. Occasionally hypotension may occur with higher dose levels. **Contra-indications** Patients with atrio-ventricular block, marked bradycardia and cardiogenic shock. **Packs** Cartons of 28 Slow-Trasicor tablets consisting of two reminder calendar foils of 14. Basic NHS price £6.66 PL0008/0130 PA 28/7/1 Full prescribing information is available on request from CIBA Laboratories, Horsham, West Sussex.
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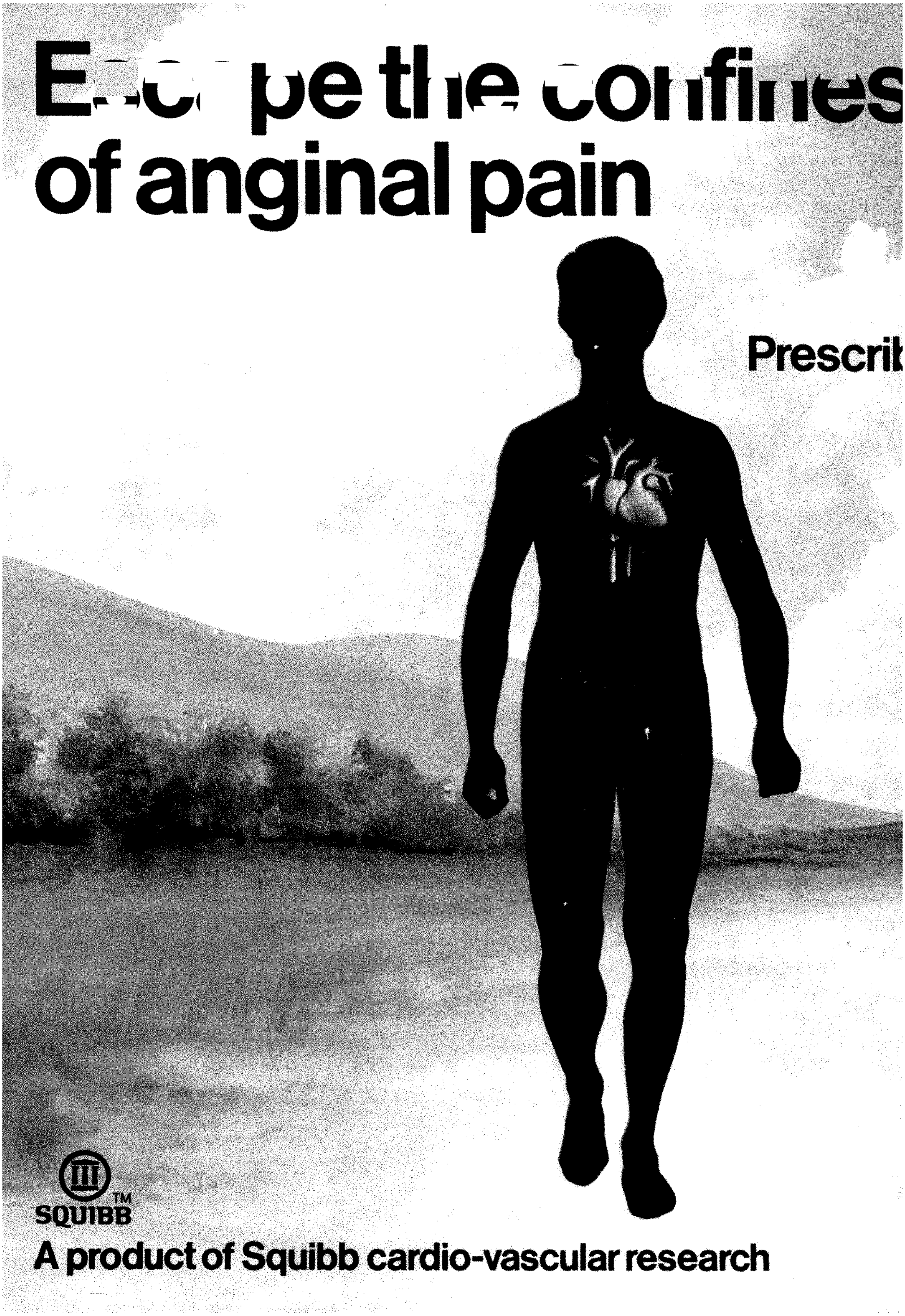

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Presentation
White round biconvex tablets. 80 mg: scored on one side and engraved "Squibb" '241' containing nadolol 80 mg. 40 mg: engraved "Squibb" '207' containing nadolol 40 mg.

Indications
Corgard is indicated in the long-term management of angina pectoris and hypertension.

Dosage and administration
Dosage should be individually titrated. In elderly patients, particularly those with angina pectoris, a low initial dose should be used so that sensitivity to side effects may be assessed.
Nadolol may be given in a once daily dosage without regard to meals.
Angina Pectoris: Initially 40 mg once daily. This may be increased at weekly intervals until an adequate response is obtained or excessive bradycardia occurs. Most patients respond to 160 mg or less daily.
The value and safety of daily doses exceeding 240 mg have not been established.
Hypertension: Initially 80 mg once daily. This may be increased by a weekly increment of 80 mg or less until an optimum response is obtained. Most patients respond to 240 mg or less, daily, but doses up to 640 mg have been required for a few patients. In some patients it is necessary to administer a diuretic, peripheral vasodilator and/or other anti-hypertensive agent in conjunction with nadolol in order to achieve satisfactory response.
Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent.

Contra-indications
Bronchial asthma, sinus bradycardia and 2nd and 3rd degree heart block; cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure.

Warnings
The normal precautions associated with the use of beta-adrenergic blockers should be followed.
Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency.
When discontinuing long-term nadolol therapy the dosage should be reduced gradually over a period of at least two weeks.
There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.
Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus.
Care should be taken in administering nadolol during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors.
The safety of nadolol in pregnancy has not yet been established, and nursing mothers should only receive nadolol if deemed essential.

Side-effects
These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. Those reported infrequently include gastro intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insufficiency, hypotension and AV block have occurred on rare occasions
Overdosage or exaggerated response should be treated supportively and symptomatically.

Legal category
Prescription only.

Product Licence Numbers
80 mg - 0034/0186
40 mg - 0034/0185

Package quantities
Bottles of 100 tablets.
Average daily cost of treatment 15p per day.

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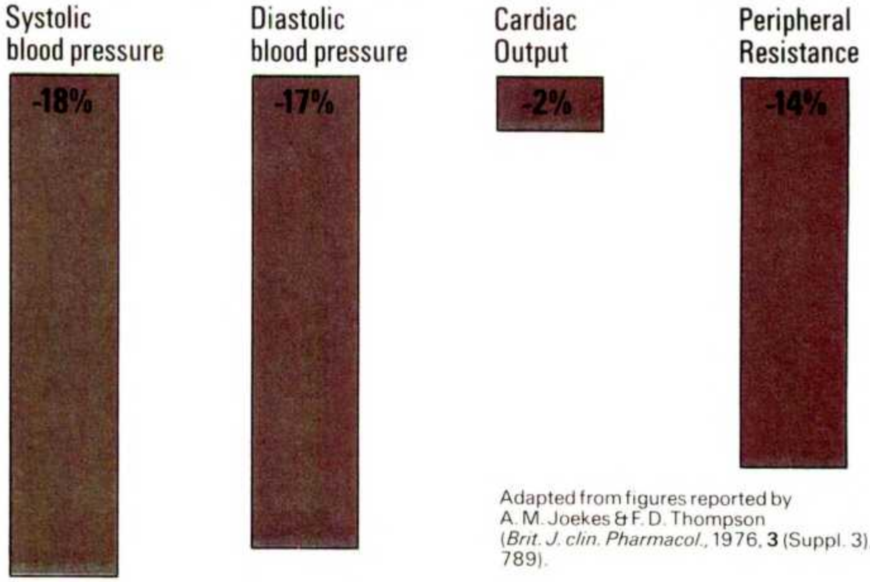
Trandate

(labetalol hydrochloride)

has the right haemodynamic profile

HAEMODYNAMIC CHANGES FOLLOWING INTRAVENOUS TRANDATE



Adapted from figures reported by A. M. Joekes & F. D. Thompson (*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

The above figure shows the mean haemodynamic changes in 14 hypertensive patients given intravenous Trandate 0.5-1.0mg/kg

In essential hypertension the usual haemodynamic changes are increased blood pressure and peripheral resistance while cardiac output remains normal.

The authors of the above trial reported:
"Although there are striking changes in the blood pressure, this can be largely attributed to a fall in peripheral resistance with little change in pulse rate, stroke volume or cardiac output."

INTRAVENOUS TRANDATE
reduces blood pressure and peripheral resistance
without significantly affecting cardiac output

come down fast...

INJECTION

Trandate Injection provides rapidly effective control of hypertensive emergencies

AS A BOLUS INJECTION...

"Labetalol given intravenously is highly effective for the acute reduction of blood pressure. In this series no serious side effects were encountered and the drug seems particularly suitable for use in hypertensive emergencies." (Rosei, E. A. et al, *Clin. Sci. mol. Med.*, 1976, **51**, 497s)

OR AS A CONTINUOUS INFUSION...

"Labetalol, given slowly by graded intravenous infusion, with continuous monitoring of arterial pressure, is our current treatment of choice in hypertensive emergencies." (Brown, J. J. et al, *Lancet*, 1977, **i**, 1147)

Subsequent treatment can be continued with the same drug given orally

"A practical advantage associated with labetalol is that oral treatment can be instituted immediately after using the intravenous form."
(Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

There are many advantages to using a compound that can be given ntravenously to control blood pressure in patients with small vessel disease or impaired renal function, which is then available for long-term oral therapy."
(Joekes, A. M. & Thompson, F. D., *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789–793)

Trandate Tablets provide effective therapy in all grades of hypertension – including the difficult cases

"In this study (oral) labetalol reduced the blood pressure significantly in a group of patients with severe, drug-resistant hypertension."
(Morgan, T. et al, *Med. J. Australia*, 1978, **i**, 393)

"Complete control of the blood pressure could hardly be expected in this group of patients and it was rewarding to obtain a very useful reduction n both the systolic and diastolic pressures in such a high percentage with a simple treatment regimen (oral Trandate)."
(Altman, M., *J. Pharmacotherapy*, 1978, **1**, 208)

Trandate

THE FIRST ALPHA-BETA-BLOCKER

RIGHT IN PRINCIPLE - WORKING IN PRACTICE

PRODUCT INFORMATION

PRESENTATION

Trandate Tablets 100mg, 200mg and 400mg each contain labetalol hydrochloride, 100mg, 200mg and 400mg, respectively. In packs of 50 and 250. PL 0045/0106, PL 0045/0107 and PL 0045/0109.
Trandate Injection: 20ml ampoules each containing 100mg (5mg/ml) labetalol hydrochloride. In boxes of 5 ampoules. PL 0045/0104.

INDICATIONS

Trandate Tablets are indicated for the oral treatment of all grades of hypertension, mild, moderate and severe. Trandate Injection is indicated when rapid control of blood pressure is essential.

DOSAGE AND ADMINISTRATION

Trandate Tablets:
Adults: The initial dosage should not usually exceed 100mg 3 times daily. Adjustment of dosage should be gradual. Most cases are controlled with 600mg per day or less, but severe cases may require up to 2,400mg daily. Administration should be after a main meal.

Trandate Injection:
Adults: When rapid reduction of blood pressure is essential a dose of 50mg of Trandate should be given by intravenous injection over at least one minute. This may be repeated, if necessary, at 5-minute intervals but the total daily dose should not exceed 200mg. Alternatively it may be given by intravenous infusion. For this 2 ampoules of Trandate Injection are diluted to 200ml with sodium chloride and dextrose injection BP. This is infused at a rate of 2ml/minute until a satisfactory response is obtained when the infusion should be stopped. For most patients the effective dose is from 50 to 200mg but in phaeochromocytoma up to 300mg may be necessary.

Patients should be in the supine position when Trandate Injection is given and they should not stand or sit up within 3 hours of starting the administration. Once controlled, blood pressure reduction can be maintained with Trandate Tablets at a starting dose of 200mg 3 times daily.
Children: Not applicable.
For information on the use of Trandate with other drugs or for transfer to Trandate from other antihypertensive agents, see respective Data Sheets.

CONTRA-INDICATIONS, WARNINGS, ETC.

Trandate should not be given to patients with uncontrolled or digitalis-resistant heart failure, or with atrioventricular block. Caution is necessary in asthmatic patients or others prone to bronchospasm. Patients with severe liver damage will probably require lower doses of Trandate than usual. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.
Trandate Injection may cause excessive postural hypotension if patients are allowed to assume the upright position within 3 hours of administration.
Trandate Tablets may cause symptoms of postural hypotension if initial dosage is too high or increased too rapidly, but they are uncommon, except at very high doses, if used as recommended. Mild and usually transient side effects include: headache, tiredness, dizziness, depressed mood, lethargy, difficulty in micturition, epigastric pain and nausea and vomiting. Tingling in the scalp has occasionally occurred but is usually transient. Rarely, a lichenoid rash has been reported which disappears on drug withdrawal. Other skin rashes, blurring of vision, eye irritation and cramps have been reported but have been difficult to relate directly to Trandate treatment.
Warning: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the drug was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.

Full prescribing information is available on request.

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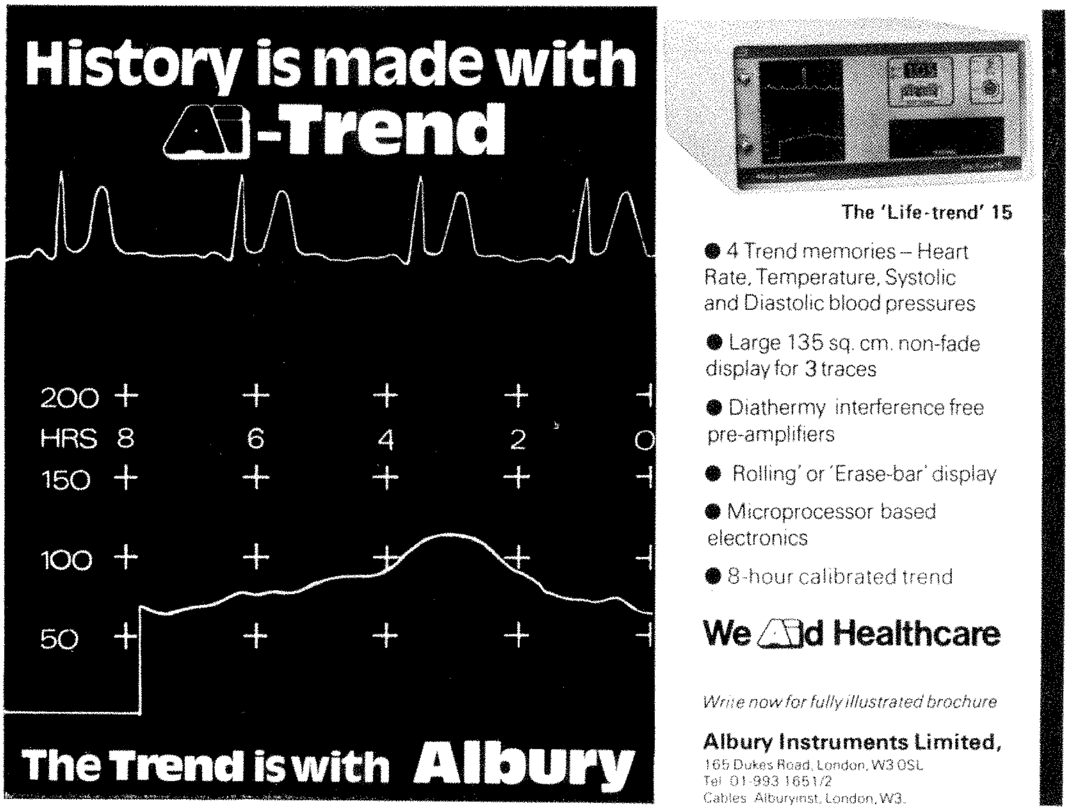

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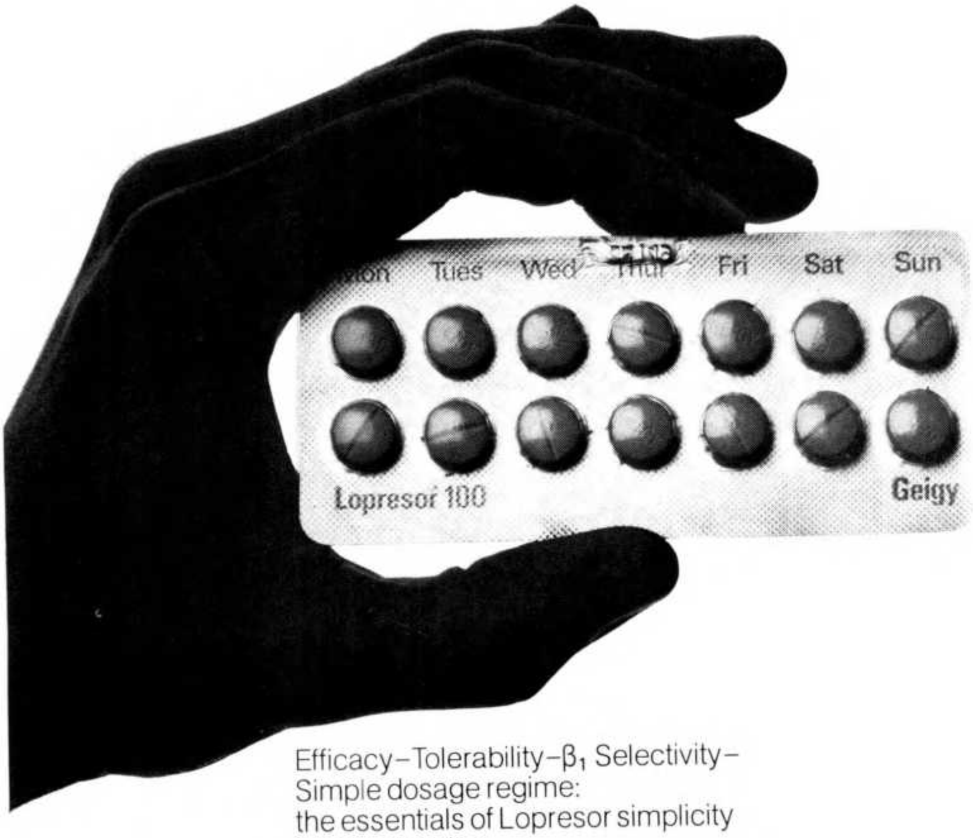

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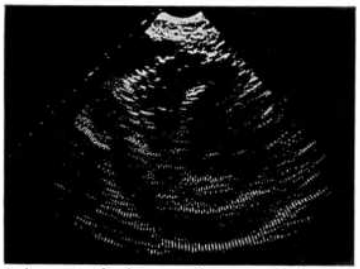
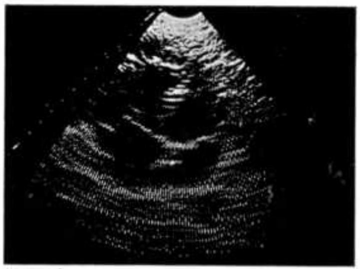

Left ventricular hypertrophy, pericardial effusion.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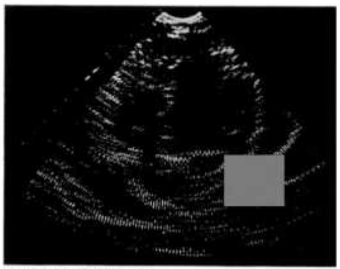
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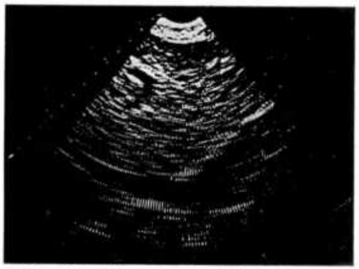
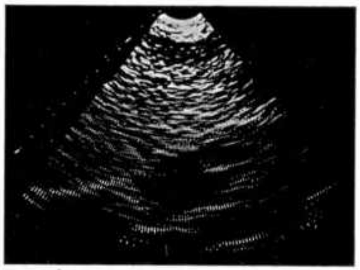

Inferior Vena Cava entering right atrium.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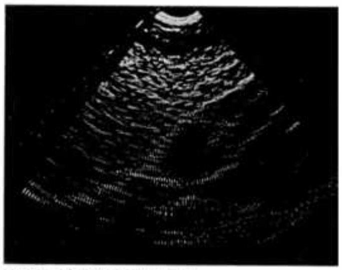
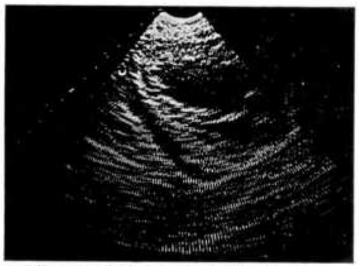
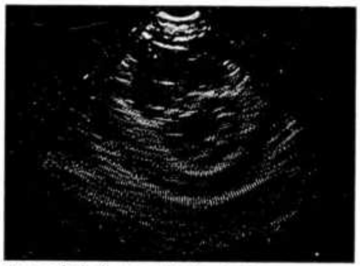
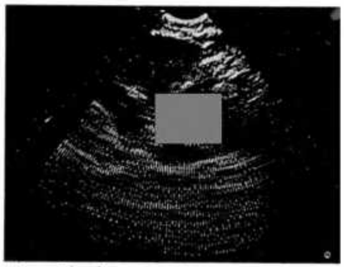

Tricuspid valve vegetation.


Small pericardial effusion, long axis view.


Pericardial effusion, short axis view.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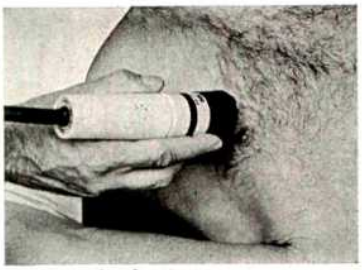
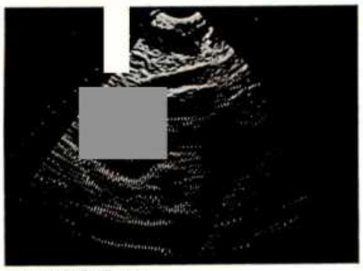
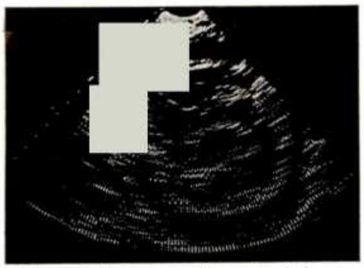
Mitral valve prolapse.


Apex Four Chamber Views


Pericardial effusion.

Subxyphoid Views


Left ventricular hypertrophy pericardial effusion, short axis.

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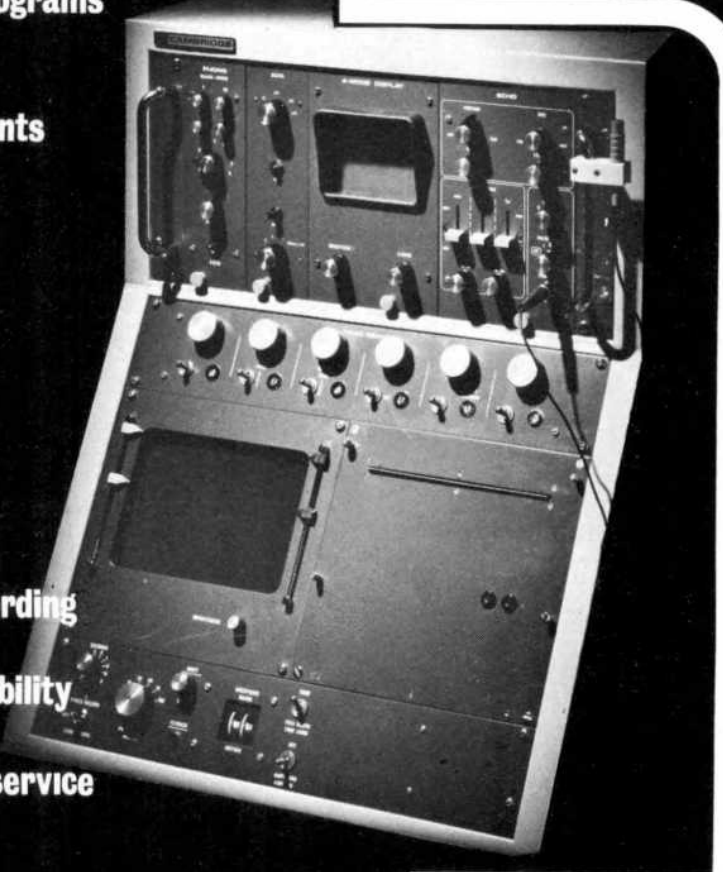

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Assessment of function of contractile segments in patients with left ventricular aneurysms by quantitative first pass radionuclide ventriculography

*Haemodynamic correlation at rest and exercise**

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SUMMARY Thirteen patients with left ventricular aneurysms complicating myocardial infarction were studied by contrast angiography and by first pass radionuclide ventriculography. The ejection fraction of the contractile segment (EFCS) was measured from both studies using a double hemispheroid model, and the values correlated closely. There was a monotonic relation between EFCS and stroke volume index measured from thermodilution cardiac outputs carried out simultaneously with the radionuclide study When radionuclide ventriculography was performed at submaximal supine exercise, changes in EFCS paralleled changes in the total left ventricular ejection fraction in 10 of the 13 cases.

In nine patients, changes in EFCS paralleled changes in stroke volume index and the relation between EFCS and stroke volume index was maintained at exercise. After administration of the vasodilator isosorbide dinitrate to 12 patients, repeat exercise radionuclide ventriculography showed an improvement in left ventricular ejection fraction and in eight patients EFCS improved.

First pass radionuclide ventriculography can accurately estimate EFCS, which may be an important factor in predicting the likely response to aneurysmectomy. Changes in EFCS on exercise are reflected in changes in total left ventricular ejection fraction and stroke volume index. Isosorbide dinitrate may improve contractile segment function on exercise.

Surgical resection of left ventricular aneurysms complicating myocardial infarction is a well-established therapeutic technique, though there are wide ranges in both the reported in-hospital mortality and the long-term mortality,[1–5] and the procedure is by no means certain to produce clinical improvement. The crucial factors in the assessment of patients being considered for aneurysmectomy are the demonstration of segmental rather than diffuse ventricular dysfunction and the presence of sufficiently good function of the contractile portion of ventricle. The differentiation between segmental and diffuse ventricular disease has for many years been accomplished by contrast left ventriculography,[6] but contractile segment function has often been assessed by visual inspection of the cineangiogram, rather than by objective quantification. Recently, attempts have been made to quantify contractile segment function angiographically and to relate this function to the risks and results of aneurysmectomy.[7 8] These studies have suggested that a contractile segment ejection fraction of approximately 40 per cent is necessary for a good result from aneurysmectomy.

The ability of radionuclide ventriculography to detect left ventricular aneurysms and to discriminate between aneurysms and diffuse hypokinesis is well documented.[9 10] This study describes the quantification of contractile segment function by radionuclide ventriculography and haemodynamic correlates of this function at rest and on exercise. The effect of isosorbide dinitrate on left ventricular function on exercise is also assessed.

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* This work was supported by the British Heart Foundation.

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Received for publication 19 June 1979

Patients and methods

Thirteen patients with left ventricular aneurysms occurring after myocardial infarction were studied. There were 11 men and two women. Their ages ranged from 44 to 64 years with a mean age of 56 years. The main reason for investigation was cardiac failure in 10, angina pectoris in two, and recurrent ventricular arrhythmias in one. Informed consent was obtained in all cases. Left heart catheterisation was performed via a right brachial arteriotomy, left ventriculography being carried out in the right anterior oblique projection. A flow-directed thermodilution catheter was positioned in the pulmonary artery. In eight patients the haemodynamic measurements were made at the time of catheterisation with the following procedure. Thirty minutes were allowed to lapse for the effects of contrast media to subside[11] and control measurements were made of cardiac output by the thermodilution technique,[12] using a Waters cardiac output computer (COR 100A), and of heart rate. All measurements were made in triplicate. The patients then performed submaximal supine leg exercise with a bicycle ergometer, at a previously determined work rate that caused a rise in heart rate of between 30 and 50 per cent over resting levels, but that did not cause limiting dyspnoea or angina pectoris. Measurements were then repeated. Submaximal exercise was employed in these patients as all were severely symptomatic. They would have been unable to maintain exercise for long enough to allow three sets of haemodynamic measurements to be made had higher workloads been used. After a 10 minute rest period, 5 mg isosorbide dinitrate were administered sublingually. Fifteen minutes after the drug, by which time resting left ventricular filling pressure had fallen to 16 mmHg or less in all patients, exercise was reperformed to the same level as previously and measurements repeated.

The other five patients were not exercised in the catheter laboratory but had all haemodynamic measurements performed at the time of radionuclide ventriculography.

A resting radionuclide ventriculogram was carried out in the right anterior oblique projection, within six hours of cardiac catheterisation in 10 patients and within 24 hours in the other three, using a computerised multicrystal gamma camera with high count-rate capabilities[13] (Baird-Atomic, System 77). A 10 mCi bolus of high specific-activity technetium^{99m}, as pertechnetate, was injected through the right atrial lumen of the thermodilution catheter with a rapid saline flush. One thousand frames of data were collected at 50 ms framing intervals to monitor the first pass of the radionuclide through the central circulation. A 1½ in parallel-hole collimator was used. Data were corrected for field non-uniformity and the dead time of the instrument, and stored on magnetic tape. The day after the resting study, radionuclide ventriculography was performed at exercise, after an identical workload in the case of the eight patients who had exercised in the catheter laboratory. The other five patients were exercised using an identical procedure, haemodynamic measurements being made immediately before the cessation of exercise and the injection of the radionuclide. In 12 of the 13 patients, a further exercise radionuclide ventriculogram was performed 15 minutes after 5 mg isosorbide dinitrate were administered sublingually, allowing at least 25 minutes between the two exercise studies. This period was allowed for the clearance of the majority of the first bolus of technetium^{99m} from the intracardiac blood pool. Before the second exercise study a static background frame was counted to a maximum of 9000 counts per cell and the second study corrected for residual blood pool activity as well as for field non-uniformity and dead time. Since constant patient positioning was crucial to enable accurate background blood pool correction, the positions of four light beams emitted by the detector head were marked on the patients' chests and adjusted as necessary before the injection of the post-isosorbide dinitrate radionuclide bolus.

There was no morbidity in any case and the maximum accumulated dose of technetium^{99m} for each patient was 35 mCi.

For this study, a ventricular aneurysm was defined angiographically as a clearly demarcated akinetic segment with or without associated areas of dyskinesis,[14] separated from a contractile segment of ventricle, in sinus rhythm. Coronary artery stenoses of 70 per cent or more of the arterial lumen were judged to be significant.

For objective evaluation of the contrast angiograms end-diastolic and end-systolic frames were traced by selecting the largest and subsequent smallest appearing ventricular outlines of a beat that was not an ectopic, or immediately after an ectopic. Analysis of the radionuclide studies was carried out using software supplied by the manufacturers. Total left ventricular ejection fraction was calculated from the change in counts from end-diastole to end-systole, read from the high frequency background corrected time-activity curve from the left ventricular region of interest,[10 15] making no assumptions about ventricular geometry. A representative cardiac cycle was generated by summing corresponding frames from the peaks and troughs of the time-activity curve. The perimeters of the ventricle at end-diastole and end-systole were generated after linear interpolation of the end-diastolic and end-systolic frames from a data matrix of 294 points (14×21) to one of 4704 points (56×84).

The computerised edge enhancement technique used for perimeter generation consisted of highlighting the 5 per cent count band corresponding to 25 to 30 per cent of the maximum end-diastolic count for both end-diastole and end-systole. This method of edge enhancement has been found to produce the most consistent agreement with contrast angiographic volumes.[10]

EFCS per cent was measured using the double hemispheroid model of Watson *et al.*[8] In this model a line of demarcation is drawn between the section of ventricle that shows definite inward motion during systole, that is the contractile segment, and the akinetic or dyskinetic segment. EFCS was calculated from an area-length method modified to fit the double hemispheroid model, with the long axis of the segment being the longest length perpendicular to the line of demarcation. The areas and lengths were calculated from the traced perimeters of both contrast and radionuclide studies, using an electronic pressure pad linked to a computer, and an algorithm analogous to planimetry. For each area and length, three measurements were taken and meaned.

Stroke volume index was calculated from the mean of the thermodilution cardiac outputs, heart rate, and body surface area. Results were analysed by Student's t test and Spearman's rank test.

Results

Aneurysms were anterolateral or apical in 12, one patient having a discrete inferior aneurysm. No patient had significant mitral regurgitation. Eight patients had one-vessel coronary disease, seven of these having an occluded left anterior descending artery, one an occluded right coronary. One had two-vessel disease and four had three-vessel disease.

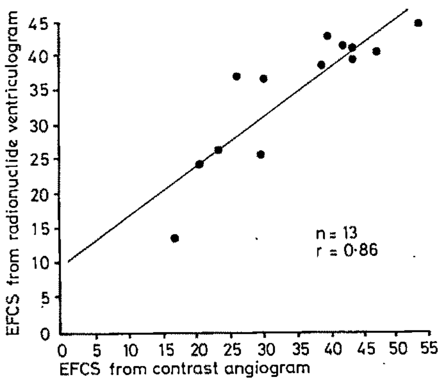

Fig. 1 *Plot of EFCS from contrast angiogram against EFCS from radionuclide study. EFCS, ejection fraction of contractile segment.*

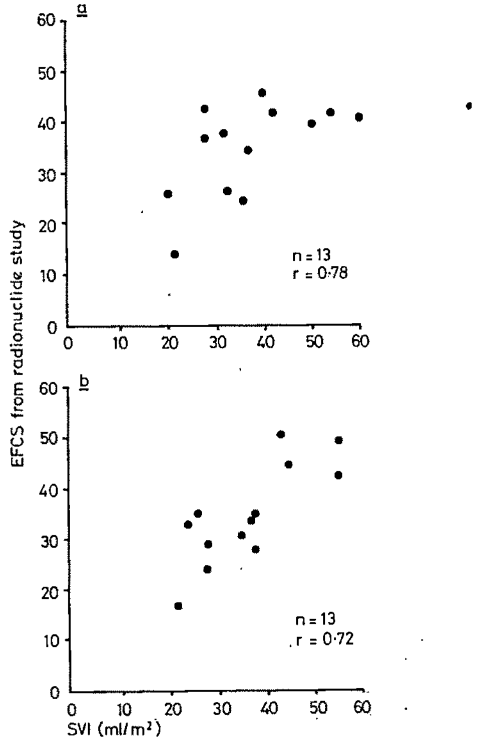

Fig. 2 (a) *Correlation between stroke volume index (SVI) and EFCS at rest.* (b) *Correlation between stroke volume index (SVI) and EFCS at exercise. EFCS, ejection fraction of contractile segment.*

EFCS from the contrast angiogram ranged from 17 to 53 per cent with a mean of 34·7 per cent, while EFCS from the radionuclide study at rest ranged from 14 to 46 per cent with a mean of 35·0 per cent. Total left ventricular ejection fraction was reduced in all patients, ranging from 19 to 37 per cent, with a mean of 27·0 per cent. The correlation between EFCS from contrast and radionuclide studies is shown in Fig. 1, the correlation coefficient being 0·86 ($p < 0·001$). There was a poor correlation between EFCS and total left ventricular ejection fraction ($r = 0·3$). Thus total left ventricular ejection fraction could not be used to differentiate patients with good and bad contractile segment function. Stroke volume index ranged from 20 to 59 ml/m², with a mean of 36 ml/m². Fig. 2a shows the relation between resting EFCS and resting stroke volume index to be monotonic. Analysis of this relation by

Spearman's non-parametric rank test shows a significant correlation with a coefficient of 0·78. This is not surprising as by definition the contractile segment is the only ventricular segment contributing to cardiac output.

Six patients had a resting EFCS of 40 per cent or more. Residual standard error from regression was used to estimate the predicted value of EFCS from the radionuclide angiogram which corresponded to a value of 40 per cent from the contrast angiogram. Thus EFCS (radionuclide) = 39·2 ±3·0 per cent at EFCS (contrast) of 40 per cent.

EFFECTS OF EXERCISE

For the whole group, left ventricular ejection fraction ranged from 16 to 40 per cent with a mean of 28 per cent, not significantly different from rest. EFCS ranged from 17 to 50 per cent with a mean of 35 per cent. All six patients who showed a rise in total left ventricular ejection fraction had an increased EFCS, and of five with a fall in total left ventricular ejection fraction, four had decreased EFCS. Only one patient had a decreased left ventricular ejection fraction with a rise in EFCS. Fig. 3 shows the changes in left ventricular ejection fraction on exercise plotted against the changes in EFCS, there being a significant correlation between the changes, whether positive or negative ($r = 0{\cdot}70$, $p < 0{\cdot}01$). Thus changes in ventricular function as assessed from the count-volume method reflect those from the geometric model using computer-generated ventricular perimeters.

Of seven with an increased stroke volume index on exercise, six had an increased EFCS. Of four with a reduced stroke volume index, three had reduced EFCS. The monotonic relation between EFCS and stroke volume index was maintained on exercise, as shown in Fig. 2b, with a correlation coefficient of 0·72 using Spearman's non-parametric rank test.

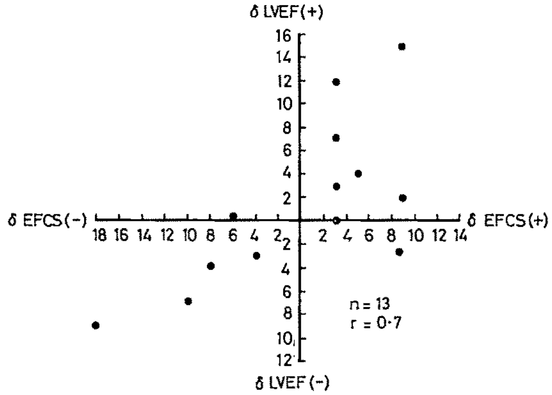

Fig. 3 *Plot of change in left ventricular ejection fraction and change in EFCS from rest to submaximal exercise. δLVEF, change in total left ventricular ejection fraction (count volume method). δEFCS, change in ejection fraction of contractile segment.*

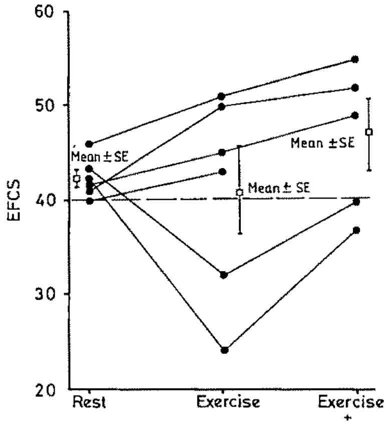

Fig. 4 *Changes in EFCS in six patients with initial EFCS of 40 per cent and more.*

Of the six patients with an initial EFCS of 40 per cent or more, four showed an increase and two a decrease at submaximal exercise. Mean EFCS for this group did not differ significantly from the resting values (Fig. 4). Of those with an initial EFCS of less than 40 per cent, four improved and three deteriorated on exercise. Again, the mean value did not differ significantly from rest (Fig. 5).

EFFECT OF CORONARY STATUS ON EXERCISE RESPONSE

Of the eight with one-vessel disease, three improved and five deteriorated on exercise. All patients with more extensive disease improved. No patient experienced angina during exercise.

EXERCISE AND ISOSORBIDE DINITRATE

At exercise after isosorbide dinitrate, left ventricular ejection fraction ranged from 22 to 44 per cent with a mean of 32 per cent. This represents a significant improvement over the pre-isosorbide dinitrate values ($p < 0{\cdot}01$, Fig. 6). Stroke volume index ranged from 29 to 74 ml/m^2, mean 41·4, significantly better than before isosorbide dinitrate ($p < 0{\cdot}005$).

EFCS ranged from 26 to 55 per cent with a mean of 38 per cent, eight patients showing an improvement, three being unchanged, and one worse than before isosorbide dinitrate, though for the whole group the improvement in EFCS failed to achieve statistical significance.

Analysis of the responses in relation to the resting EFCS shows that of the five patients with resting EFCS of 40 per cent or more who received isosorbide dinitrate, all improved, with a mean EFCS for this subgroup of 46·6 compared with 40·9 before isosorbide dinitrate (Fig. 4). This improvement achieves statistical significance ($p < 0{\cdot}025$). Of the seven with an EFCS of less than 40 per cent at rest, three improved after isosorbide dinitrate, one worsened, and three remained unchanged after isosorbide dinitrate (Fig. 5). All three who improved achieved a higher EFCS than at rest. Mean EFCS was 32·0 after isosorbide dinitrate, compared with 29·2 before the drug, an improvement that is not statistically significant.

Fig 7 relates the changes that occurred in the two exercise periods to the changes that occurred from rest to exercise. Of the seven patients in whom EFCS improved from rest to exercise, six improved further after isosorbide dinitrate and one worsened. Of the five who deteriorated from rest to exercise, two improved and three were unchanged after isosorbide dinitrate. Thus a bad response to exercise did not preclude a good response to isosorbide dinitrate, though a good response to exercise was more likely to predict a good response to isosorbide dinitrate.

Fig. 8 shows an example of how contractile segment function may improve after isosorbide dinitrate. The left-hand image shows the perimeters for the pre-isosorbide dinitrate study, the right shows them post-isosorbide dinitrate. The end-diastolic perimeter is shown in white, the end-systolic perimeter in yellow. It is evident that the contractile segment shows greater inward motion in the right-hand image, and the calculated EFCS has correspondingly increased. The contractile segment and the aneurysmal segment are both clearly seen in each image.

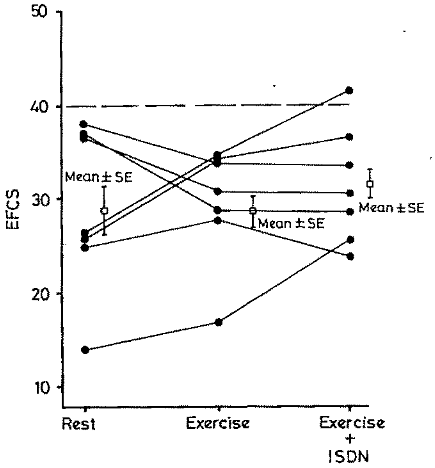

Fig. 5 *Changes in EFCS in seven patients with initial EFCS of less than 40 per cent. EFCS, ejection fraction of contractile segment.*

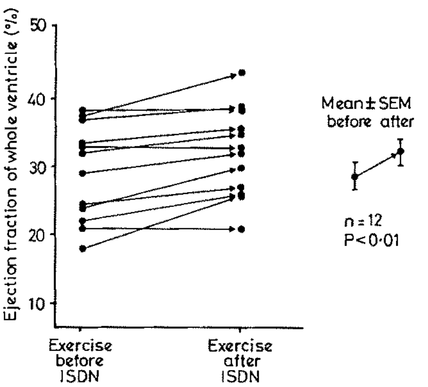

Fig. 6 *Exercise left ventricular ejection fraction (LVEF) before and after isosorbide dinitrate (ISDN). SEM, standard error of the mean.*

EFFECT OF CORONARY STATUS ON ISOSORBIDE DINITRATE RESPONSE

Of the eight patients with one-vessel disease, five improved after isosorbide dinitrate and three remained unchanged. Of those who improved, three had shown an improvement from rest to exercise. Four of the five who improved had a resting EFCS of 40 per cent or more. Of those with three-vessel disease, three improved and one worsened. All had shown an improvement from rest to exercise and only one had a resting value of EFCS of 40 per cent or more.

These results suggest that the response to isosorbide dinitrate is not governed entirely by coronary status, inasmuch as the four non-responders contained three with one-vessel disease.

Discussion

Resection of left ventricular aneurysms is now a well-recognised surgical procedure, but it has become evident that not only is surgical mortality high in some series,[4 5] but clinical improvement is by no means the rule.[5] Key *et al.*[16] commented on the necessity for 'good left ventricular deep constrictor activity' to increase the likelihood of a successful operation. In 1971, Kluge *et al.*[17] described an unquantified relation between 'the quality of basal myocardial contractility' and immediate postoperative survival. More recently, these subjective relations have been superseded by objective methods for quantification of basal or contractile segment function from contrast angiograms.[7,8]

The importance of a method for objective quantification of contractile segment function is evident, as total left ventricular ejection fraction at rest was unable, in this study, to differentiate bad from good contractile segment function, an observation in agreement with Watson *et al.*[8] All patients had reduced total left ventricular ejection fraction, however. The double hemispheroid model is easily applicable to the image produced by superimposition of the ventricular perimeters (Fig. 8) but is not the only method available. Arthur *et al.*[7] calculated EFCS by excluding the aneurysmal portion of ventricle from the cineangiogram and redrawing the cardiac border as a fixed elliptical line equidistant from the longitudinal axis as the opposite contracting border. Lee *et al.*[18] expressed the contractility of the non-aneurysmal ventricular segment as the difference between actual ejection fraction and that predicted from the spherical model of Feild *et al.*[19] The double hemispheroid technique was chosen for this study as it has been validated against geometric models of known volumes, and the sums of subchamber volumes have been shown to correlate with total ventricular volumes.[8]

The relation between EFCS and stroke volume index (Fig. 2) is further testimony to the validity of the model as applied to the radionuclide study. Though others have reported no correlations between EFCS and cardiac index,[8] this latter depends on another variable, heart rate, as well as on stroke volume.

The rationale behind separating those patients with an EFCS of 40 per cent or more from those with a value of less than 40 per cent is based on the findings that an EFCS of less than 44 per cent in one study,[8] or less than 38 per cent in another,[7] predicted a poor surgical result. It is implied, therefore, that an EFCS of below approximately 40 per cent means a critical impairment of residual ventricular function.

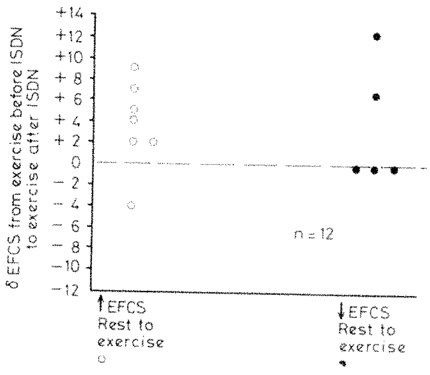

Fig. 7 *Changes in EFCS from exercise before to after isosorbide dinitrate (ISDN) related to changes in EFCS from rest to exercise. EFCS, ejection fraction of contractile segment.*

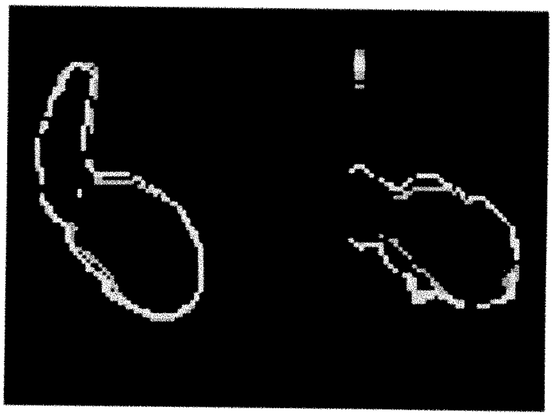

Fig. 8 *Superimposed end-diastolic (white) and end-systolic (yellow) perimeters generated from the radionuclide ventriculogram by edge enhancement (see text). Left-hand image, exercise before isosorbide dinitrate (EFCS 24%). Right-hand image, exercise after isosorbide dinitrate (EFCS improved to 36%).*

The short data acquisition time required for a first pass radionuclide ventriculogram means that studies on exercise are not limited by changes in the stability of patients' circulatory status, all data collection being completed within one minute from the cessation of exercise.

Borer *et al.*[20] have previously shown that no significant differences occurred in ejection fraction or regional ventricular function when sequential exercise radionuclide ventriculograms were performed with no intervention. This was the case for both normals and patients with coronary artery disease. The parallel changes between radionuclide and haemodynamic data described in this study support the findings of Borer *et al.*[20] that changes seen after an intervention are not the result of intrinsic errors in the method used.

The changes in ventricular function, as measured by total left ventricular ejection fraction, were variable and were paralleled by changes in contractile segment function in 10 of the 13. The limitations of comparing results from a single plane geometric model with results from a three-dimensional measurement of radioactive counts may contribute to the discrepancies in the other three. It is possible that changes detected in the right anterior oblique may have been offset by opposing changes in the areas of the contractile segment not visualised in that projection, whereas this will not affect measurement of total left ventricular ejection fraction. The same problem will apply to comparisons of changes in EFCS and stroke volume index. The variable changes in left ventricular ejection fraction, EFCS, and stroke volume index that occurred on exercise are consistent with the spectrum of exercise responses described in other studies, in which wide ranges in the responses of stroke volume index, cardiac index, and left ventricular stroke work index occurred in patients with cardiac failure.[21 22]

Improvement in ventricular function on exercise may be brought about by augmented myocardial contractility under the inotropic stimulus of exercise and, indeed, the failing ventricle may be hypersensitive to circulating catecholamines.[23] Conversely, the increase in peripheral vascular tone and hence ventricular afterload may be poorly tolerated by the failing ventricle because of the rise in systolic wall tension and myocardial oxygen consumption.[24] Thus, the changes in EFCS, like the changes in stroke volume index, may be affected by multiple opposing factors and provide angiographic correlates of previously reported variable haemodynamic changes.

The failure of more than half the patients with single-vessel disease to improve EFCS on exercise, despite apparently normal residual coronary anatomy, is worthy of comment. It is possible that in the chronically dilated and overstretched ventricle excessive myofibrillar slippage leads to an often irreversible depression of contractility[25] which is independent of coronary status.

Ischaemia of the contractile segment would not appear to play an important role in determining the response to exercise in view of the good response of those with extensive coronary disease. In addition, no patient experienced angina pectoris during exercise.

In recent years, dramatic improvements in the performance of the failing left ventricle have been shown after the administration of vasodilator drugs. Oral isosorbide dinitrate has been shown to be effective in causing a substantial reduction in left ventricular filling pressure in patients with congestive cardiac failure.[26 27]

The results of this study indicate that sublingual isosorbide dinitrate may lead to improvements in global and segmental ventricular function on exercise, with significant improvements in total left ventricular ejection fraction for the group as a whole, though the changes in EFCS were only statistically significant in those with a resting EFCS of greater than 40 per cent. In the other group, the changes in EFCS paralleled those in left ventricular ejection fraction and stroke volume index but did not achieve statistical significance. In four patients in the study (33%) EFCS failed to improve, however.

The detected improvement in exercise EFCS after isosorbide is consistent with the improvement in exercise haemodynamics that has been previously reported in patients with both diffuse impairment of left ventricular function[22] and with left ventricular aneurysms.[28] In both these studies, isosorbide dinitrate caused significant improvements in ventricular stroke work index and stroke volume index, and significant reductions in left ventricular filling pressure on exercise.

It has been suggested that the principal action of vasodilators in general is to reduce left ventricular afterload[29] with a concomitant reduction in myocardial wall tension. The reduction in filling pressure may be also partly a result of a fall in preload produced by venodilatation.[30] The reduced wall tension leads to an increased velocity of myocardial fibre shortening.[31] In addition, the effects of the inotropic stimulation occurring on exercise may be enhanced by the pharmacological reduction of wall tension leading to greater augmentation of cardiac performance.[32]

It is of interest that the more consistent response to isosorbide dinitrate took place in the patients with the higher resting EFCS and the improvement was significant in this group but not in those with an EFCS of less than 40 per cent. A previous study has shown that the improvement in exercise cardiac index was related directly to the resting EFCS.[22] Nevertheless, improvements in EFCS did occur in four out of seven patients with an EFCS of less than 40 per cent. It is also of note that responses to isosorbide dinitrate could not be entirely predicted on the basis of the rest to exercise changes, though of the eight who improved after isosorbide dinitrate, six had shown an improvement on exercise.

Again, coronary status did not appear to be of paramount importance in governing the response to isosorbide dinitrate, there being a similar spectrum of response in those with single or multiple vessel disease. The possibility does exist, however, of redistribution of blood by the nitrate to ischaemic areas in the contractile segment,[33] though the evidence that such alterations in regional blood flow do occur in man is by no means conclusive.

Left ventricular aneurysmectomy may or may not lead to an improvement in exercise tolerance and left ventricular end-diastolic pressure[5]; so a method that could predict the likely results of surgical resection in terms of mortality and of clinical improvement would be welcome.

One hopes that the pharmacological improvements in EFCS, left ventricular ejection fraction, and stroke volume index brought about by the vasodilator would mimic the beneficial haemodynamic effects of reducing ventricular filling pressure by aneurysmectomy, though further prospective and postoperative studies are required before a pharmacological intervention can be extrapolated to the surgical situation with any confidence. Contractile reserve, as measured by response to isosorbide dinitrate, does exist even in those patients with a low resting EFCS, though apparently to a lesser extent than in those with higher EFCS. Conversely, a resting EFCS of 40 per cent or more does not always indicate good contractile reserve, since some such patients will have had a bad response to exercise, and may not achieve resting levels even after isosorbide dinitrate. Even patients with one-vessel coronary disease may fall into this category possibly because of irreversibly damaged muscle in the contractile segment despite normal residual perfusion. It remains to be seen at what level of response, either good or bad, the surgical result becomes unacceptably poor.

In summary, computerised first pass radionuclide ventriculography provides a simple and safe way of assessing segmental and global ventricular function at rest and exercise. The double hemispheroid model is applicable to computer-generated ventricular outlines and detected changes in contractile segment function parallel changes in simultaneously recorded haemodynamics. If the function of the contractile segment is the prime factor in determining the result of aneurysmectomy, then stress radionuclide ventriculography can provide unique angiographic data to aid in selection of patients for aneurysmectomy.

The demonstration that isosorbide dinitrate can improve exercise ventricular function suggests that the drug may improve exercise tolerance in some patients with left ventricular aneurysms. This technique may allow more logical identification of patients likely to benefit from long-term nitrates when aneurysmectomy is not contemplated or contraindicated.

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Br Heart J 1980; **43**: 134–137

Haemodynamic effects of prenalterol in patients with coronary heart disease

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SUMMARY The haemodynamic effects of prenalterol, a new selective beta-1 adrenoreceptor agonist, have been studied in patients with coronary heart disease. The drug was administered intravenously in a dosage of 0·5 to 2·5 μg/kg body weight to 20 patients undergoing coronary angiography and to 10 patients with a recent myocardial infarction, who had clinical evidence of left ventricular dysfunction. Left ventricular performance was enhanced in both groups of patients—left ventricular dP/dt (max) increased by 33 per cent and the systolic time intervals, pre-ejection period, and the ratio of pre-ejection period and left ventricular ejection shortened by 28 and 21 per cent, respectively. Cardiac output and stroke volume increased with no change in heart rate nor in left ventricular filling pressure. These results indicate that prenalterol enhances the contractile state of the myocardium without altering heart rate, and suggest that prenalterol could be of value in the management of patients with coronary heart disease, who have impaired left ventricular function.

The hospital mortality associated with acute myocardial infarction appears to result from pump failure which is related to the extent of myocardial necrosis. Such patients have been shown, both at angiography and at necropsy, to have triple vessel coronary artery disease and to have 45 to 50 per cent of the myocardium damaged.[1–3] Sympathomimetic amines have been used in the management of such cases and also to provide inotropic support after cardiac surgery. Noradrenaline increases cardiac contraction but produces intense peripheral and coronary arterial vasoconstriction resulting in increased myocardial oxygen consumption.[4] Isoprenaline is a potent beta-adrenoreceptor agonist but increases heart rate in addition to its inotropic action. The deleterious side effects of the sympathomimetic amines have stimulated research into pharmacological compounds which can exert inotropic effects but have little chronotropic action. Dobutamine has been shown both in man[5] and in the experimental animal[6] to have a significant inotropic action, but in patients after open heart surgery, though an inotropic action was shown, there was a similar chonotropic effect to that of isoprenaline.[7] Dopamine has been shown to be a useful inotropic agent particularly as it dilates the renal arterial circulation, but some workers have suggested that it produces ventricular arrhythmias. Prenalterol, the laevoisomer of S-(-)-1-(4 hydroxyphenoxy)-3-isopropylamino-propanol-2 hydrochloride, is a new selective beta-1 adrenoreceptor agonist which has been shown in animal pharmacological studies by Carlsson *et al.*[8] to have little chronotropic effect. Johnsson *et al.*[9] have reported in human volunteers that prenalterol, when administered both orally and intravenously, results in an increase in myocardial contractility and has little or no effect on heart rate.

Received for publication 21 August 1979

The object of the present study was to assess the cardiovascular effects of prenalterol in patients with coronary heart disease undergoing coronary angiography and in patients with a recent myocardial infarction who had clinical evidence of left ventricular dysfunction.

Patients and methods

Twenty male patients with coronary heart disease undergoing coronary angiography were studied at the time of cardiac catheterisation. The patients were all in sinus rhythm and beta-adrenoreceptor blocking agents had been discontinued 48 hours before investigation. Those receiving cardiac glycosides were excluded from the study. Ten patients with acute myocardial infarction who were being treated in an intensive coronary care unit and who were considered to have clinical evidence of left ventricular dysfunction, as evidenced by tachycardia, additional heart sounds, and lung base crepitations, were also studied by non-invasive techniques, systolic time intervals, and echocardiography. The nature of the study was carefully explained to each patient and their consent was obtained. Approval for the study had also been obtained from the hospital ethical committee.

HAEMODYNAMIC STUDY

A high fidelity left ventricular pressure recording was obtained using a Millar transducer tipped catheter (PC-350). The catheter has a flat frequency response from 0 to 250 kHz. The left ventricular pressure wave form was recorded on a frequency modulation instrumentation tape recorder and subsequently analysed on a PDP-8 computer. The computer digitised 8 seconds of recorded signal at a rate of 250 samples per second.. The rate of rise of pressure dP/dt was then calculated between successive samples from end-diastole to peak systole, and dP/dt (max) and dP/dt over simultaneously developed pressure (P) was then determined for each beat analysed (dP/dt/P).[10] The results presented are the mean values of all beats within an 8 second sample. Heart rate was obtained from a continuous recording of the electrocardiogram, systemic blood pressure was measured from the Millar catheter, and cardiac output was determined using a thermodilution technique (Instrumentation Laboratories). All cardiac outputs were done in triplicate and the mean of the results was taken.

Non-invasive study

The systolic time intervals total electromechanical systole (QS_2), left ventricular ejection time (LVET), pre-ejection period (PEP), and ratio of PEP/LVET were measured from simultaneous high-speed recordings of the electrocardiogram, phonocardiograms, and carotid pulse wave tracing.[11] Each interval was measured to the nearest 5 ms, mean values of six cardiac cycles being obtained. Blood pressure was measured by sphygmomanometer. Echocardiographic measurements of the left ventricle were recorded.[12] End-diastolic and then end-systolic volumes of the left ventricle were calculated and stroke volume derived. Heart rate was monitored from a continuous recording of the electrocardiogram.

Experimental procedure

In the haemodynamic study after baseline measurements prenalterol was infused intravenously in doses of 0·5 to 2·5 μg/kg body weight per minute. The drug was dissolved in dextrose and infused over a five to eight minute period using a calibrated infusion pump (Sage Instruments). Each patient received two intravenous infusions of prenalterol on consecutive occasions separated by approximately five minutes.

Results

HAEMODYNAMIC STUDY

The detailed results are noted in Table 1.

dP/dt (max) increased to a maximum of 30 per cent at an infusion rate of 1·5 μg/kg from 1788 ±146 to 2393 ±206 mmHg/s ($p < 0{\cdot}01$) and there was no further increase at higher rates of infusion. dP/dt/P increased from 78 ±1 to 93 ±4 s^{-1} ($p < 0{\cdot}01$). Left ventricular end-diastolic pressure did not change, 10 ±2 to 9 ±1 mmHg. There was little change in heart rate until the maximum rate of infusion of 2 μg/kg per min when there was a non-significant increase from 79 ±5 to 85 ±4 beats/min. Systolic blood pressure was little altered, 133 ±11 and 132 ±13 mmHg, but diastolic blood pressure fell from 81 ±5 to 76 ±6 mmHg. Cardiac output increased from 5·2 ±0·4 to 6·1 ±0·4 l/min ($p < 0{\cdot}05$). There was a corresponding increase in stroke volume from 72 ±11 to 79 ±10 ml ($p < 0{\cdot}05$).

MYOCARDIAL INFARCTION STUDY

The detailed results are found in Table 2.

In this group of patients there was little change in heart rate until the maximum rate of infusion of 2·5 μg/kg per min from 83 ±8 to 95 ±5 beats/min. The pre-ejection period (PEP) significantly shortened from 114 ±10 to 91 ±7 ms, representing a 20 per cent increase in myocardial contractility at an infusion rate of 2 μg/kg per min, when there was no change in heart rate. Left ventricular end-diastolic volume was unaltered, 90 ±8 and 97 ±6 ml, as was mean arterial blood pressure, 98 ±7 and 97 ±7 mmHg.

A linear relation between the increases in dP/dt and PEP/LVET and the log of plasma concentrations of prenalterol was not apparent (Fig.). Significant enhancement of myocardial contractility was found with plasma levels of 40 to 50 mmol/l and there was little further effect with increasing plasma levels. Plasma concentrations of prenalterol were assayed in the research laboratories of AB Hässle, Gothenburg, Sweden.

SIDE EFFECTS

There were no obvious side effects, specifically no adverse biochemical effects or evidence of hepatic or renal impairment.

Table 1 *Haemodynamic study*

Dosage regimen	*Heart rate (beats/min)*	*Systolic BP (mmHg)*	*Diastolic BP (mmHg)*	*Mean BP (mmHg)*	*Cardiac output (l/min)*	*Stroke volume (ml)*	*dP/dt (max) (mmHg/s)*	*dP/dt/P* (s^{-1})	*LVEDP (mmHg)*
Control	64 ±4	134 ±3	80 ±2	96 ±4	5·8 ±0·2	100 ±6	1649 ±132	32 ±2	10 ±2
0·5 µg/kg body weight per min n=7	65 ±3	136 ±3	77 ±2	95 ±5	6·2 ±0·1	108 ±5	1993 ±205*	39 ±4*	9 ±3
Control	85 ±3	136 ±4	81 ±3	98 ±4	—	—	1949 ±142	72 ±4	9 ±3
1·0 µg/kg body weight per min n=8	88 ±2	137 ±5	77 ±4	96 ±5			2546 ±187†	90 ±6†	7 ±4
Control	76 ±3	133 ±11	81 ±5	97 ±6	5·2 ±0·4	72 ±11	1788 ±146	78 ±1	10 ±2
1·5 µg/kg body weight per min n=9	79 ±4	132 ±13	76 ±6	93 ±7	6·1 ±0·4*	79 ±10*	2393 ±206†	93 ±4†	9 ±1
Control	79 ±5	130 ±15	75 ±8	92 ±5	5·7 ±0·3	75 ±9	2145 ±210	87 ±6	9 ±1
2·0 µg/kg body weight per min n=8	85 ±4	131 ±17	72 ±9	90 ±5	5·8 ±0·4	74 ±8	2208 ±193	90 ±5	9 ±1

Results are mean ±SEM. $^*p < 0{\cdot}05$. $^\dagger p < 0{\cdot}01$.

Table 2 *Myocardial infarction study*

Dosage regimen	*Heart rate (beats/min)*	*Systolic BP (mmHg)*	*Diastolic BP (mmHg)*	*Mean BP (mmHg)*	QS_2 *(ms)*	*LVET (ms)*	*PEP (ms)*	*PEP/LVET*	*LVEDV (ml)*
Control	73 ±4	138 ±5	98 ±6	111 ±8	371 ±14	277 ±10	102 ±8	0·3504 ±0·0096	101 ±52
1·0 µg/kg body weight per min	76 ±4	134 ±8	80 ±6	98 ±7	346 ±12	266 ±9	81 ±8*	0·3037 ±0·0288*	113 ±50
Control	73 ±4	127 ±10	85 ±7	99 ±9	401 ±22	309 ±13	100 ±10	0·325 ±0·035	102 ±47
1·5 µg/kg body weight per min	73 ±6	141 ±7	87 ±5	105 ±7	368 ±22	283 ±20	85 ±12*	0·3065 ±0·0538*	118 ±52
Control	76 ±6	129 ±10	82 ±5	98 ±7	402 ±20	289 ±24	110 ±17	0·4079 ±0·1154	90 ±8
2·0 µg/kg body weight per min	76 ±7	132 ±12	79 ±5	97 ±7	360 ±22	260 ±26	100 ±10*	0·4039 ±0·0639*	97 ±6
Control	83 ±8	128 ±10	76 ±4	93 ±6	356 ±18	241 ±13	114 ±40	0·477 ±0·26	89 ±10
2·5 µg/kg body weight per min	95 ±5	133 ±6	81 ±4	98 ±5	317 ±18	226 ±11	91 ±7*	0·4013 ±0·0236*	79 ±7

Results are mean ±SEM in 10 patients. $^*p < 0{\cdot}05$.

Discussion

The data obtained from this study suggest that prenalterol has a significant inotropic action in patients with coronary heart disease with little or no effect on heart rate. The invasive measurements of dP/dt (max) and dP/dt/P have been shown to be acceptable indices of myocardial contractility and to be relatively insensitive to changes in left ventricular filling pressure and ventricular afterload.[13] In this study the heart rate was unaltered, left ventricular end-diastolic pressure was unchanged, as was systemic blood pressure and thus the significant increases in dP/dt (max) and dP/dt/P indicate that prenalterol has a positive inotropic action. This increase in the contractile state of the myocardium was also reflected by the significant increases in cardiac output and stroke volume.

Although prenalterol appears to exert a positive inotropic action in patients with coronary artery disease with normal or only modest impairment of left ventricular function, its application might be more relevant to an acute pathology such as a recent myocardial infarction. Thus it seemed appropriate to investigate the drug in patients with acute myocardial infarction, who had clinical evidence of left ventricular dysfunction. The assessment of ventricular function in these patients was by means

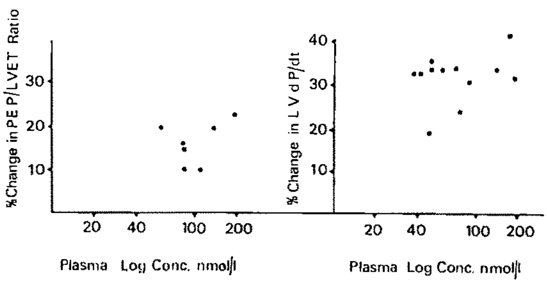

Fig. *The relation between the percentage change in dP/dt and pre-ejection period and the log of prenalterol plasma concentrations.*

of non-invasive techniques, systolic time intervals, and echocardiography. The duration of the pre-ejection period in the absence of changes in preload or afterload is a determination of the rate of rise of left ventricular pressure during isovolumic contraction.[14] The ratio of PEP/LVET correlates closely with the ejection fractions measured by ventriculography.[15] In this study there was a significant shortening of the PEP and a decrease in PEP/LVET ratio indicating enhanced contractility. There was no change in heart rate or in systemic blood pressure. Echocardiography suggested that there was no change in left ventricular end-diastolic volume and this significant reduction in both PEP and PEP/LVET ratio indicates that prenalterol appears to enhance myocardial contractility in patients with a recent myocardial infarction, who had evidence of left ventricular dysfunction. In both groups of patients the changes in myocardial contractility did not seem to be dose related, enhancement of myocardial contractility being noted with relatively low circulating plasma levels of the drug. In patients with significant left ventricular dysfunction it may be that larger doses of prenalterol might be needed to produce a similar effect and thus increase cardiac output.

Many agents which are used to provide inotropic support are arrhythmogenic and must be used with caution in the patient with acute cardiac infarction. In this small group of patients no arrhythmias were observed despite careful electrocardiographic monitoring, and even in the presence of significantly raised plasma levels of prenalterol. These results found in patients with coronary heart disease are similar to those found in healthy patients,[9] even on exercise, where arrhythmias were not found after the administration of prenalterol.

Hypotension and cardiac failure are the principal causes of death in patients with acute cardiac infarction treated in a coronary care unit, and positive inotropic agents, which are not arrhythmogenic and cause little increase in heart rate either alone or in combination with vasodilator treatment, might be of value in reducing the mortality in this group of patients. However, the greatest potential use for this beta-1 adrenoreceptor agonist with positive inotropic and little chronotropic effect appears to be in the postoperative cardiac surgical patient and in the management of patients with coronary heart disease, who have chronic congestive cardiac failure.

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Br Heart J 1980; **43**: 138–142

Mechanism of influence of PR interval on loudness of first heart sound

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SUMMARY It is well known that the loudness of the first heart sound is influenced by the duration of the PR interval and the position of the atrioventricular valve cusps at the moment of ventricular contraction, but the exact mechanism of this phenomenon has not been explained satisfactorily.

In this study, high speed echophonocardiograms were used to correlate the timing of mitral valve closure with the electrocardiogram and heart sounds in 67 normal subjects. Measurements were made of the PR interval and of the delay between the onset of ventricular depolarisation and mitral valve closure (Q-MC). To permit comparison of sound intensity between individuals, the amplitude of the mitral component of the first sound (M1) was compared with that of the aortic component of the second sound (A2) in the same subject.

When the PR interval was very long, mitral valve closure occurred soon after the onset of the electrocardiogram QRS complex, and there was no accompanying sound. Since the Q-MC interval in these cases was less than the electromechanical interval of 40 ms, the valve was already closed before the onset of ventricular contraction and closure must have been effected by atrial contraction and relaxation. With PR intervals of less than 180 ms mitral closure was audible as a sharp sound coinciding with echocardiographic closure and occurring after the onset of ventricular contraction as judged by a Q-MC of 40 ms or more; the shorter the PR interval the later and louder the mitral closure sound. Thus a primary determinant of the intensity of M1 is the timing of mitral closure in relation to the left ventricular pressure pulse. A full length PR interval gives time for coaptation of the mitral leaflets and closure occurs early as soon as left ventricular pressure starts to rise and the resulting sound is soft. A shorter PR interval, however, results in a wide open valve at the moment of ventricular contraction and hence delay in reaching its final closing halt which, therefore, occurs on a later and steeper part of the left ventricular pressure pulse and the sound is loud.

The effect of PR interval on the loudness of the first heart sound was first described in atrioventricular block[1 2]; its importance as a major influence on the character of the sound in patients with conducted sinus rhythm was appreciated some time later.[3 4] It is widely acknowledged that the effect is mediated through the partial atrioventricular valve closure induced by atrial contraction and relaxation, so that with a short PR interval the valve leaflets are widely separated, and with a long PR interval they are nearly apposed, when ventricular contraction begins.[5 6] When one considers the small mass of the valve leaflets, however, it is difficult to understand why distance of travel alone, with implied variation in closing velocity, should cause such great variations in loudness. It has been suggested that the critical factor is the timing of valve closure in relation to the ventricular pressure pulse,[7 8] but correlation between this timing and the loudness of the first sound has not previously been demonstrated in man. There are a number of possible explanations for the difficulty in establishing such a relation. Because of the differing sound transmission properties of the lungs and chest wall, direct comparison of phonocardiograms between one person and another is not meaningful. In addition, alterations in the time between the onset of ventricular contraction (or electrical depolarisation) and valve closure are likely to be small and detectable only by sensitive techniques. Finally, it is frequently difficult to

Received for publication 9 March 1979

identify separately the mitral and tricuspid contributions to the first sound on conventional phonocardiograms.[9]

The present study has used high-speed simultaneous recordings of the echo and phonocardiogram to study the effect of atrioventricular conduction time on the timing of mitral valve closure and its corresponding component of the first heart sound (M1) in normal subjects. An attempt to overcome the problem of calibrating the sound recording has been made by comparing the amplitude of M1 with that of the aortic component of the second sound, A2.

Methods

Sixty-seven normal subjects were studied. Their ages ranged from 19 to 56 (mean 32) years and there were 27 men and 40 women.

The three standard bipolar limb leads of the electrocardiogram were recorded at 100 mm/s paper speed and at four times normal calibration (1 mV=40 mm). The lead showing the earliest QRS deflection was selected for recording with the echocardiogram and phonocardiogram.

Echocardiograms were recorded with a Smith-Kline Ekoline 20 ultrasonoscope (2·25 MHz focused transducer, pulse repetition frequency 1850 s^{-1}) interfaced with a Cambridge six-channel photographic recorder which had been modified to double echo depth magnification and with the maximum recording speed increased to 200 mm/s. The mitral valve was identified by the standard technique, and transducer angulation and position were adjusted to demonstrate the moment of valve closure, defined as the point of complete apposition of its anterior and posterior leaflets.

A high frequency phonocardiogram was recorded simultaneously with the echocardiogram using a Cambridge crystal microphone attached to the skin by suction. The microphone was placed accurately over the apex beat and the sensitivity of the amplifier was adjusted so that whenever possible both the first and second heart sounds could be recorded. The recordings were made in shallow held expiration, with maximal magnification of the echo display and at a film speed of 200 mm/s.

The PR interval was measured on the simultaneous standard lead electrocardiogram recording from the earliest P wave onset to the earliest deflection of the QRS complex. The mean value was determined from five cardiac cycles measured to the nearest 0·5mm (5 ms). The time from the electrocardiogram Q wave to mitral valve closure (Q-MC) was measured on the echocardiogram to the nearest 0·5 mm (2·5 ms) using a hair-line cursor. Five cardiac cycles were measured and the average value expressed to the nearest millisecond. The mitral component of the first sound (M1) was identified on the phonocardiogram from the exact coincidence of its onset with the earliest point of coaptation of the anterior and posterior cusps of the mitral valve on the echogram (Fig. 4). The peak-to-peak amplitude of the maximum trace deflection was measured and from this the width of the baseline (2·5 mm) was subtracted. The maximum amplitude of the aortic component of the second sound (A2) was determined in the same manner. From these measurements the M1/A2 amplitude ratio was determined from the mean of five consecutive cycles.

Results

The mitral valve echogram was suitable for analysis in every case. Satisfactory phonocardiograms were recorded in 58 subjects.

In six subjects, all with PR intervals equal to or exceeding 180 ms, no sound occurred at the time of mitral valve closure. In all the others valve closure was synchronous with the onset of the sound.

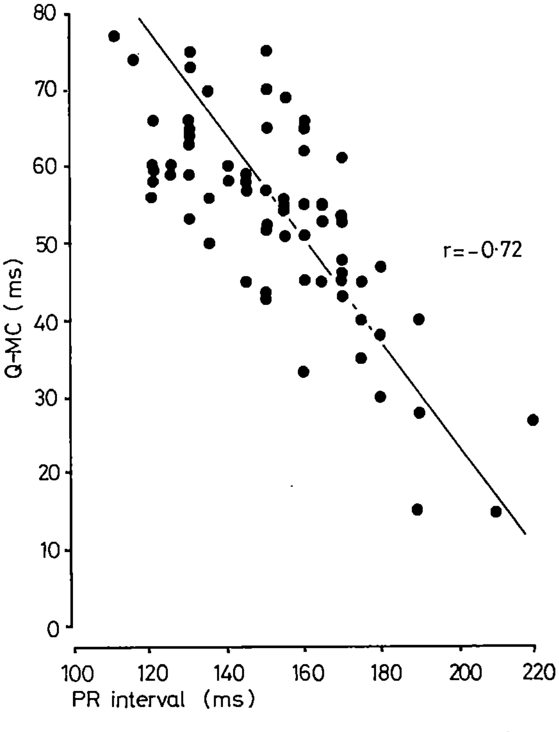

Fig. 1 *The influence of PR interval on the timing of mitral valve closure.*

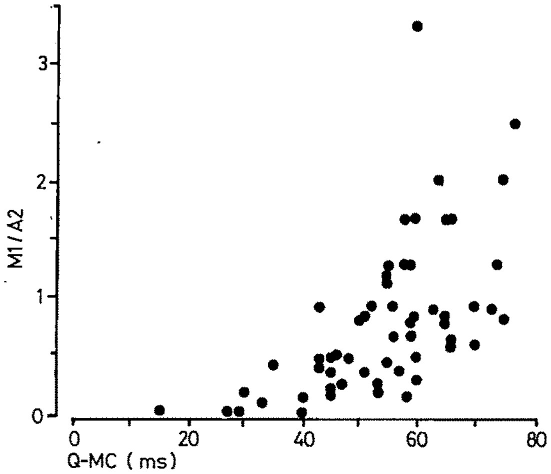

Fig. 2 *The relation between the amplitude ratio M1/A2 and the timing of mitral valve closure (Q-MC).*

The influence of PR interval on the timing of mitral valve closure and M1 is described in detail elsewhere.[9] When the PR interval was long the valve leaflets were almost apposed at the time of ventricular depolarisation and Q-MC was short. With short PR intervals the valve was still widely open at the onset of the QRS complex and Q-MC was long. This relation between PR interval and Q-MC is shown in Fig. 1, from which it can be seen that for a PR interval of 180 to 190 ms Q-MC is about 40 ms, which is approximately the time between the initiation of depolarisation and the onset of left ventricular contraction.[10 11] Thus, with PR intervals of 180 ms or greater, mitral valve closure occurs before the onset of ventricular contraction and is brought about entirely by atrial contraction and relaxation, while with shorter conduction times closure is completed after the beginning of ventricular contraction.

The relation between Q-MC and the ratio M1/A2 is shown in Fig. 2. Early mitral closure resulting from a long PR interval was associated with a small ratio and late valve closure in the presence of a short PR interval with a large ratio. When Q-MC fell to less than about 35 ms no M1 was recorded (that is mitral closure was silent) and the ratio was zero. Fig. 3 shows the recordings from two subjects aligned on the Q wave of the electrocardiogram to illustrate these findings. In the first trace the PR interval is 110 ms, Q-MC is 77 ms, and a large amplitude M1 is recorded. In the second recording from a subject with a PR interval of 170 ms, Q-MC is 48 ms and M1 has a very small amplitude. With M1/A2 expressed as a logarithm the relation of log M1/A2 with Q-MC was examined by linear regression analysis. The correlation was highly significant (r=0·65; p<0·001), and is shown in Fig. 4.

In Fig. 3, the closing velocity of the anterior mitral valve leaflet is obviously faster in the subject with a short PR interval and a loud first sound than in the individual with a long PR interval and a soft first sound, but there was no overall correlation between closing velocity and M1/A2 ratio. This is slightly surprising because such a relation has been observed in individual patients with complete heart block.[12] However, since the closing mitral valve inscribes a curved line it is quite difficult to determine its velocity immediately before the point of complete closure, and we suspect that closing velocity is related to first sound amplitude, even though we have not been able to show it.

Discussion

By using a high recording speed we have been able to detect small differences in the timing of mitral

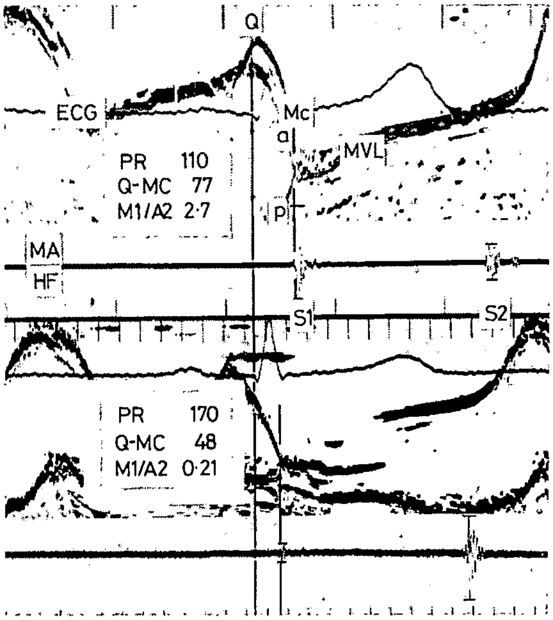

Fig. 3 *Echophonocardiograms from two subjects aligned on the Q waves of the electrocardiogram (ECG) to illustrate the influence of PR interval on the timing of mitral valve closure and the amplitude of M1 relative to A2 (see text). The onset of the P wave is not clearly defined on these recordings; PR interval was measured on the separate simultaneous recording of the three standard leads.*

a, anterior cusp of mitral valve; p, posterior cusp of mitral valve. The maximum sound deflections are marked by short horizontal bars.

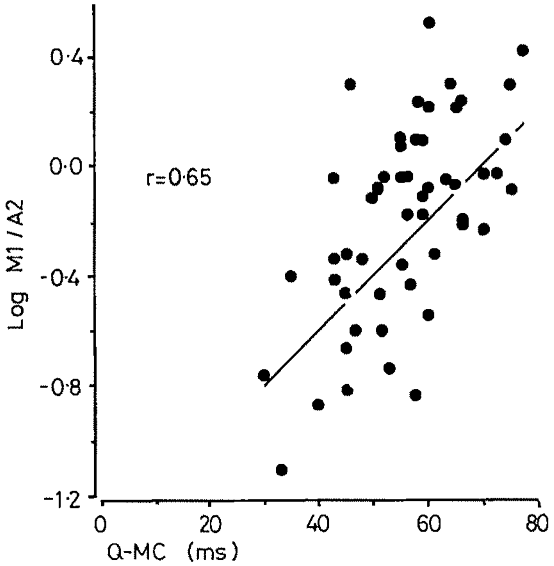

Fig. 4 *The relation between log M1/A2 and the timing of the mitral valve closure (Q-MC).*

valve closure and its corresponding component of the first heart sound (M1) associated with variations in the PR interval on the electrocardiogram. Use of the echo to identify M1 is essential because under certain circumstances the first sound may be produced solely by tricuspid valve closure, mitral closure being silent.[6 9] Furthermore, the method allows differentiation of M1 from the low-frequency vibrations which commonly precede it.

The major difficulty in studying any particular influence on the amplitude of heart sounds is the wide variation in anatomical factors which affect sound transmission from the site of production to the surface of the chest. We have attempted to overcome the problem by comparing the amplitude of M1 with that of the aortic component of the second sound (A2) at a fixed point on the praecordium, since both are affected by the same influences during their transmission to the surface. The validity of the study clearly rests on the assumption that the sound energy of A2 is constant in a group of resting normal subjects. The loudness of A2 is known to be influenced by arterial pressure, the rate of pressure fall in late systole, and the physical properties of the aortic valve and root[13]; it was thought to be a fair assumption that these factors were 'normal' in our subjects though there must be some degree of biological variation. On this premise the energy of M1 was estimated by measuring the ratio of its amplitude compared with that of A2, with the microphone placed over the apex beat. An immediate criticism is that variations in the loudness of M1 may be associated with changes in its frequency, an alteration which would, itself affect transmission through the body tissues.[13] Furthermore, the different frequency spectra of M1 and A2 result in different degrees of attenuation during their transmission to the body surface. However, these criticisms do not invalidate our results, since variations in the amplitudes of A2 and M1 unrelated to PR interval would tend to scatter the results, rather than improve the correlation we have shown. Clearly, the method cannot be applied if the aortic valve is diseased or if left ventricular ejection dynamics are altered by peripheral, myocardial, or conduction abnormalities.

The effect of PR interval on the timing of mitral valve closure has been discussed elsewhere[9]; our observations support the conclusions of others, namely that when the PR interval is longer than 180 to 200 ms, valve closure is brought about entirely by atrial activity and before the left ventricle starts to contract.[5 6 12] In the present investigation with a PR interval of 180 to 190 ms, when presystolic valve closure was complete, the M1/A2 ratio fell to zero because of the total disappearance of M1. With shorter PR intervals valve closure occurred later in relation to the onset of QRS (and, therefore, later in relation to the onset of left ventricular contraction), and was associated with the production of a sound: the shorter the PR interval, the later valve closure, and the louder the sound. This concept of loudness being associated with lateness, widely accepted for mitral stenosis,[14] has now been shown to be true also in normal subjects. We have confirmed the fact that closure of the mitral valve from the wide open position produces a loud sound and from a semiclosed position a soft sound.[5 6] These differences are not directly the result of distance of travel of the cusps (always difficult to understand), but of varying delay related to distance of travel. This is in agreement with the concept put forward by McKusick[15] and supported by Stept *et al.*[8] that the critical factor determining the loudness of the sound is the change in momentum as blood being accelerated towards the left atrium is suddenly checked by the valve closure. The momentum of the blood is determined by the force acting on it (ventricular pressure) and the time over which the force acts. Thus the wider the separation of cusps the greater the delay in coming to a final halt and the louder the sound. We believe that it is the delay consequent upon the distance of travel which causes the final halt of the valve to be later, at a point where the rate of rise of the ventricular pressure pulse is steeper, and it is therefore the delay which is responsible for the increase in intensity of the first sound associated with a short PR interval.

GL and NB were supported by British Heart Foundation Research Fellowships.

The work described is part of a study submitted by NB to the University of London for the degree of Doctor of Medicine.

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Br Heart J 1980; **43**: 143–147

Pulsed Doppler echocardiography for diagnosis of ventricular septal defects

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SUMMARY In order to assess the performance of pulsed Doppler echocardiography and to examine the factors affecting its reliability for the diagnosis of ventricular septal defects, 51 patients, in whom angiographic studies had recently been performed, were investigated before and after operation by this technique. The diagnosis was correct in all cases with left-to-right shunt, when the defect was located either in the upper muscular or in the infracristal portion of the septum, even when pulmonary hypertension or additional cardiac malformations were present. Pulsed Doppler echocardiography did not differentiate between supracristal ventricular septal defects and obstruction of the right ventricular outflow. Apical muscular defects were never observed in our cases. Defects of the inlet portion were not localised by the method. In cases with bidirectional shunt, pulsed Doppler echocardiography failed to provide any diagnostic clue. When a right-to-left shunt was present, only in one case with membranous pseudoaneurysm could pulsed Doppler echocardiography provide an exact description of the haemodynamics before and after operation. In 12 of 22 patients with tetralogy of Fallot, pulsed Doppler echocardiography showed flow tracings possibly related to the septal defect. The site of defect and the extent and direction of intracardiac shunting seem to be the main factors affecting its diagnostic performance in ventricular septal defects.

Detection of ventricular septal defect by means of M-mode and/or bidimensional echocardiography is usually possible only when the defect is either large or associated with peculiar anatomical malformations, such as aortic dextroposition. Size and shape of the ventricular chambers and of the left atrium provide indirect information about the intracardiac haemodynamic situation.[1] Bidimensional echocardiography can differentiate between ventricular septal defects and single ventricle complexes.[2]

Pulsed Doppler echocardiography, by providing information about the direction and the type (laminar vs. disturbed) of flow within the cardiac cavities and the great arteries, may prove to be a very sensitive diagnostic method for the diagnosis of ventricular septal defects. Encouraging results were reported in previous studies.[3–5]

In this paper the data on preoperative angiocardiographic and echocardiographic examinations are compared with the description of the actual malformation, as observed at the time of cardiac surgery, and with the postoperative echocardiographic controls.

Received for publication 3 May 1979

Subjects and methods

Fifty-one patients, who had previously undergone cardiac catheterisation and who were scheduled for corrective open-heart surgery, were investigated by means of 'integrated echocardiography', including M-mode, bidimensional, and pulsed Doppler examinations, employing a wide-angle sector scanner (Varian V-3000) and a Doppler echocardiograph (ATL 500 A). The pulsed Doppler echocardiographic investigation was performed with the transducer applied on the praecordium. In order to recognise defects in different areas of the septum, the transducer was directed in the following way: (a) from the apex toward the aortic root along the echoes arising from the ventricular septum, as shown in the M-mode display, for identification of muscular or infracristal septal defects; (b) toward the tricuspid valve, to recognise defects located in the upper posterior aspect of the ventricular septum; and (c) rotating the transducer caudad, after recognition of the pulmonary valve, to identify supracristal defects.

In normal subjects, when the sample volume is located within the muscular septum, a low-pitched thumping sound can be heard.[6] Time interval histogram and analogue display do not show any flow signal. Disturbed flow in this area, as indicated by a harsh sound and by a wide dot pattern on the baseline, suggests shunting between the ventricles.[7 8]

Direct inspection of the heart at the time of operation confirmed the presence of a ventricular septal defect in all patients, either uncomplicated or associated with other malformations. In 15 patients the defect was uncomplicated, in two it was associated with an atrial septal defect, in two with tricuspid regurgitation, and in five with obstruction to the right ventricular outflow. In the remaining patients the ventricular septal defect was a component of a complex malformation: three patients were confirmed to have a complete atrioventricular canal, one a left ventricle to right atrium communication, one a membranous septal pseudoaneurysm, and 22 a tetralogy of Fallot.

Postoperatively, an integrated echocardiographic investigation was repeated to allow comparison of the new echocardiographic findings with those obtained before surgery.

Results

For better evaluation of our findings, three different intracardiac haemodynamic conditions will be considered separately.

(a) LEFT-TO-RIGHT SHUNTS

When the sample volume was located within the interventricular septum, a typical turbulence was recorded in all cases with defects of the muscular and infracristal type (Fig. 1). The defect was clearly identified by pulsed Doppler echocardiography even in six patients with pulmonary hypertension where the pulmonary artery pressure was higher than two-thirds of the systemic pressure. In three patients with a supracristal defect, pulsed Doppler echocardiography showed a systolic turbulence located in the right ventricular outflow tract, similar to that seen in cases with obstruction of the right ventricular outflow. When the septal defect was located in the inlet portion, as in the three patients with complete atrioventricular canal, systolic turbulence was detected behind the cusps of the tricuspid valve. In four patients with uncomplicated ventricular septal defect, where the pulmonary to systemic flow ratio was greater than 3, mild systolic tubulence was detected in the right pulmonary artery, despite the absence of any obstruction of the right ventricular outflow. After surgical correction of the septal defect, these findings disappeared in all cases.[9] Patients with ventricular septal defect and tricuspid regurgitation showed findings indicative of both the septal defect and valve regurgitation (Fig. 2). In the case of left ventricular right atrial communication a turbulent flow behind tricuspid valve echoes was recorded during systole.

(b) BIDIRECTIONAL SHUNTS

In two patients who had previously undergone a pulmonary artery banding, haemodynamic re-evaluation showed a bidirectional shunt. The pulsed Doppler echocardiographic investigation did

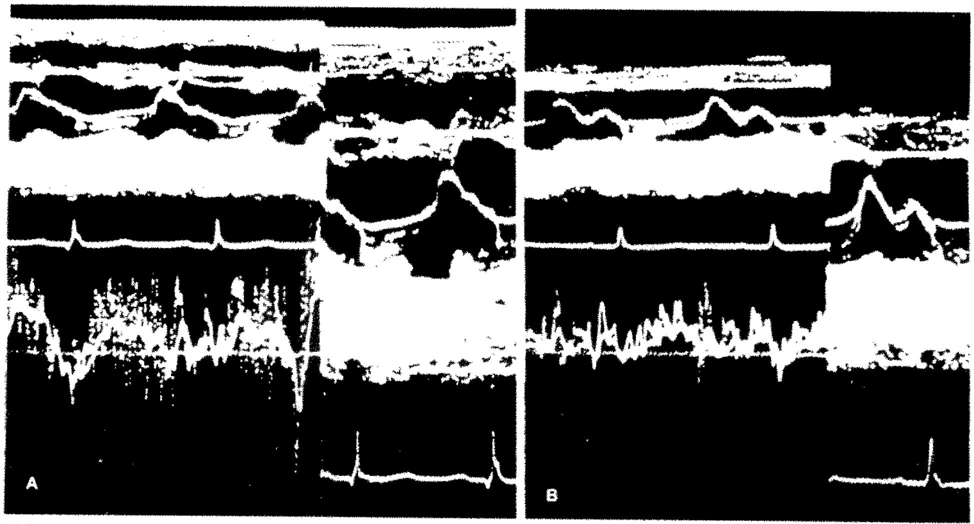

Fig. 1 *Muscular ventricular septal defect: a systolic turbulence related to shunting is recorded* (A), *which is not detectable in the postoperative control* (B).

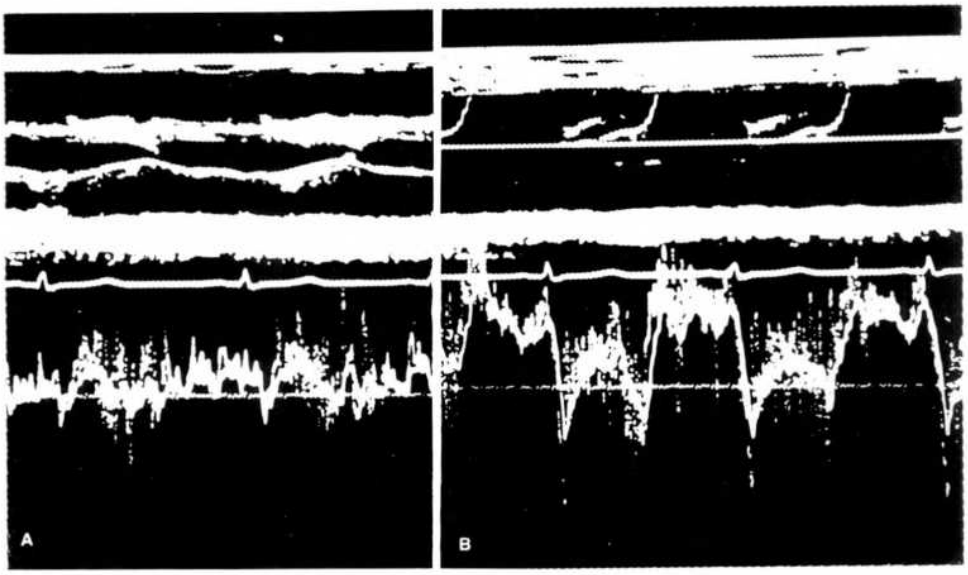

Fig. 2 *Infracristal ventricular septal defect with tricuspid regurgitation: systolic turbulence is recorded within the septum, in the subaortic portion* (A), *and behind the anterior cusp of the tricuspid valve* (B).

not provide any diagnostic clue in these cases, while bidimensional echocardiography detected the absence of a wide portion of the ventricular septum (Fig. 3). However, these two patients are not included in our series since their condition did not indicate corrective surgery.

(c) RIGHT-TO-LEFT SHUNTS

In 12 patients with tetralogy of Fallot, with the aorta fairly dextroposed, when the sample volume was located within the basal portion of the ventricular septum (as shown by M-mode display) a systolic negative wave was recorded, indicating blood flowing away from the transducer (Fig. 4). In the remaining 10 patients in this group pulsed Doppler echocardiography did not provide any information related either to the location of the ventricular septal defect or to the direction of intracardiac shunting. In the patient with a pseudoaneurysm of the membranous septum and pronounced obstruction of the right ventricular outflow, pulsed Doppler echocardiography showed a distinct systolic turbulence when the sample volume was located in the area where M-mode echocardiography detected an aneurysmal dilatation bulging toward the left ventricle in systole (Fig. 5). With the suprasternal approach a disturbed flow was detected in the ascending aorta. At surgical inspection, an accessory tricuspid cleft cusp was present, partially inserted onto the rim of the ventricular septal defect.

In all subjects, postoperative pulsed Doppler echocardiography showed the disappearance of the

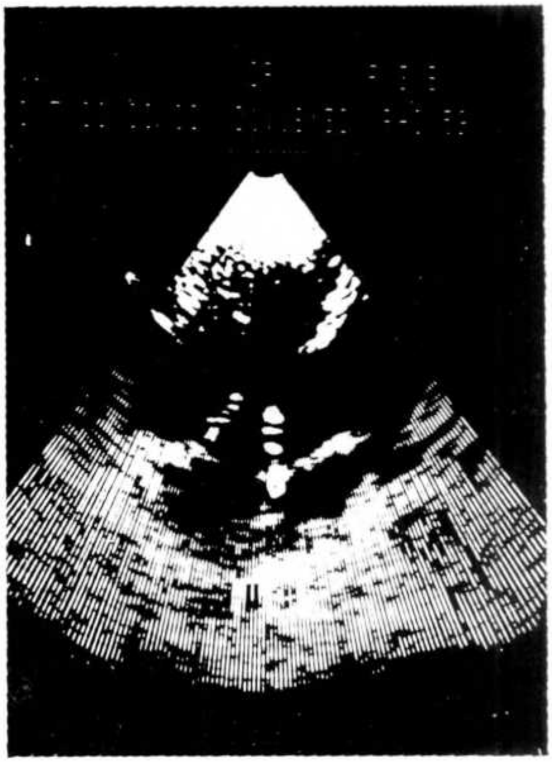

Fig. 3 *Bidimensional image (apical approach) showing absence of an ample portion of the ventricular septum in a patient with bidirectional shunt.*

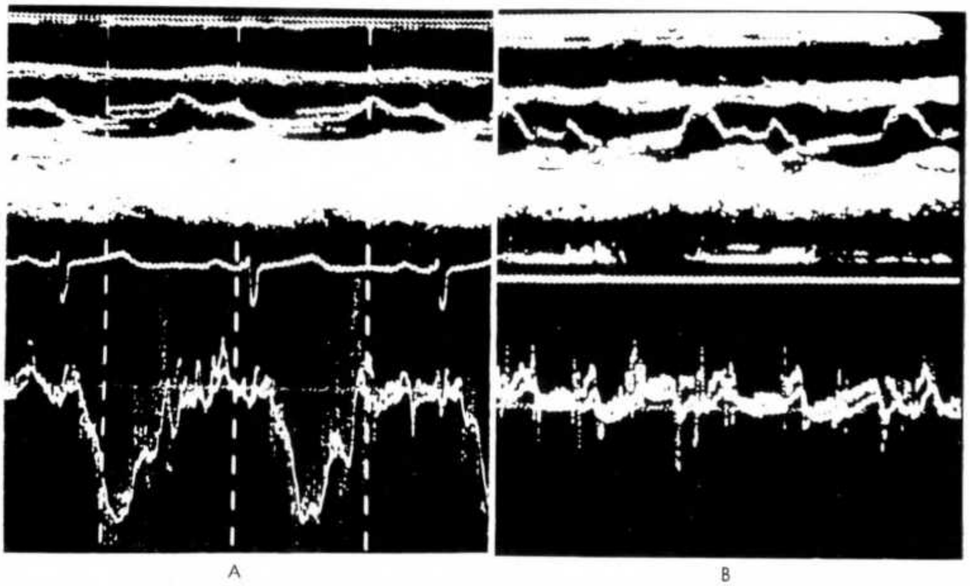

Fig. 4 *Tetralogy of Fallot: a systolic negative deflection is detected in the preoperative control* (A), *which is not recorded postoperatively* (B).

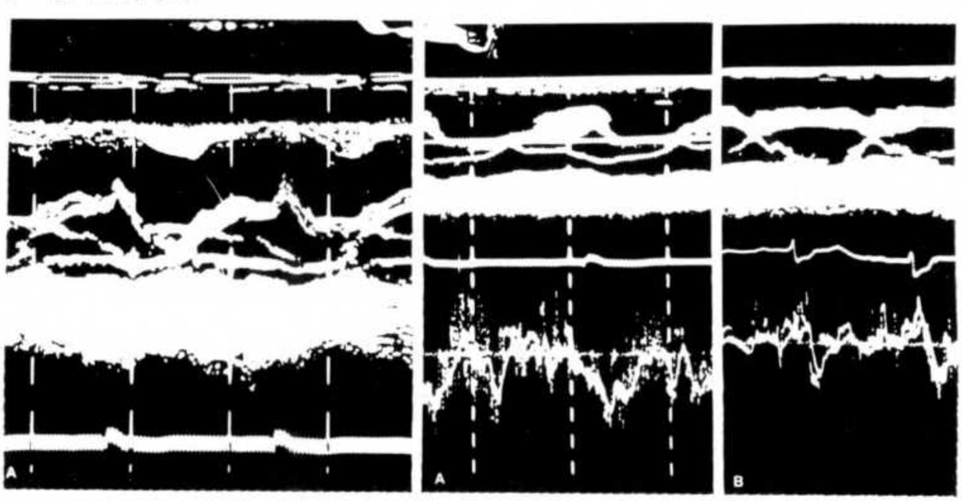

Fig. 5 *Membranous pseudoaneurysm: systolic turbulence is recorded at the level of the septal aneurysmal bulging* (A). *Postoperative recordings show disappearance of both aneurysmal bulging and systolic turbulence* (B).

preoperative findings related to ventricular septal defect.

Discussion

The site of the defect and the intracardiac haemodynamics are the main factors affecting the performance of pulsed Doppler echocardiography for the diagnosis of ventricular septal defects. In our experience, all patients with defects either of muscular or of infracristal type were correctly diagnosed by means of pulsed Doppler echocardiography even when pulmonary hypertension (with left-to-right shunt) or associated malformations (two patients with atrial septal defect, two with tricuspid regurgitation, three with right ventricular outflow obstruction) were present. Thus, our paper confirms the result of previous investigations. The typical diagnostic clue is the recording of a turbuletn flow when the sample volume is correctly located within the interventricular septum. The sign has to be highly specific: in our experience in both

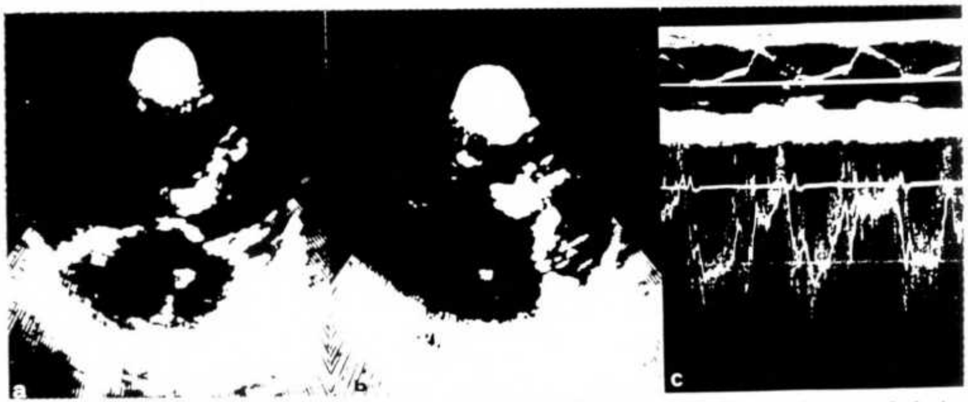

Fig. 6 *Complete atrioventricular canal (Rastelli type A). Bidimensional image by the apical approach during systole* (A) *and diastole* (B): *systolic-diastolic turbulence is recorded behind the anterior cusp of the tricuspid valve* (C) *similar to that observed in one case of partial atrioventricular canal*

normal subjects and in patients with various heart conditions it was never detected as an occasional finding. We did not see apical defects of the muscular septum during our study.

Supracristal, or distal infundibular, septal defects were characterised by a harsh systolic turbulence into the outflow tract of the right ventricle close to the echoes of the pulmonary valve. A similar finding was recorded in patients with obstruction of the right ventricular outflow: thus pulsed Doppler echocardiography does not allow differential diagnosis between the two conditions.

In patients with complete atrioventricular canal a systolic turbulence could be detected behind the echoes from the tricuspid valve (Fig. 6). We believe that this turbulent flow is related to shunting between the left ventricle and the right atrium through the mitral cleft, in the absence of the septum primum. In patients with atrial septal defects a turbulence behind the tricuspid valve is usually recorded at the telesystolic and protodiastolic phases.

In patients with complete atrioventricular canal the ventricular septal defect was clearly shown by bidimensional echocardiographic examination from the apical approach. Bidimensional echocardiography detected ventricular septal defects in patients with bidirectional shunt, while pulsed Doppler echocardiography did not provide any diagnostic information in these cases.

Bidimensional examination indicated the presence of ventricular septal defects in all patients with tetralogy of Fallot. In some of these cases pulsed Doppler echocardiography showed a blood flow toward the aortic outflow, through the basal portion of the septum, that might have been related to right-to-left shunting.

Our results suggest that pulsed Doppler echocardiography is an important complement of M-mode and bidimensional echocardiography in the diagnosis of septal defects of both the upper muscular and the 'membranous' types. Further improvement of pulsed Doppler echocardiography will be achieved when technological developments allow location of the sample volume on a bidimensional display, thus enabling this diagnostic tool to be more widely used.

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Br Heart J 1980; **43:** 148–158

Scanning suprasternal echocardiography

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SUMMARY Scanning suprasternal echocardiography was performed in 280 patients with a variety of cardiac anomalies. By using the special suprasternal transducer on the suprasternal notch, the aortic arch, right pulmonary artery, and left atrium were recorded superoinferiorly. From this reference position various scanning techniques were made to record the main pulmonary artery, pulmonary valve, ascending aorta, aortic valve, and distal aortic arch, wherever possible. These scans made it possible to assess (a) the integrity and size of right pulmonary artery and main pulmonary artery in pulmonary atresia, stenosis of origin of right pulmonary artery, pulmonary artery banding, kinked Waterston anastomosis, and aneurysm of pulmonary artery; (b) relative positions of aortic valve and pulmonary valve in malposition complexes; (c) the position and size of the aortic arch in tetralogy of Fallot and aortic coarctation. Measurements of the left atrium made by suprasternal echocardiography were consistently larger than those made by praecordial echocardiography. Changes in relative sizes of aortic arch, right pulmonary artery, main pulmonary artery, and left atrium were also documented in the various cardiac anomalies. The atrial baffle after Mustard repair for d-transposition of the great arteries and the atrial membrane in cor triatriatum were also demonstrated. The introduction of scanning techniques has thus widened the scope of suprasternal echocardiography.

Since the original description of suprasternal echocardiography,[1] more recent reports have confirmed its usefulness in clinical practice. Petsas *et al.*[2] reported its use in detecting left atrial myxomas. Allen *et al.*[3] assessed the relative size of aortic arch and right pulmonary artery, and left atrial dimensions in various cardiac malformations, and Mortera *et al.*[4] assessed the use of contrast echocardiography for the diagnosis of transposition of the great arteries. In this paper we report experience of its routine use over the past two years and of a new scanning procedure which appears to enhance the usefulness of the technique.

Subjects and methods

Two hundred and eighty patients, ranging from premature infants to young adults (Table 1) with a variety of congenital and acquired heart lesions had conventional praecordial echocardiograms. Particular attention was paid to the recording of the left atrium, aortic root, and main pulmonary artery. Left atrial dimension (LAp) was measured in end-systole from the anterior aspect of the endocardium of the left atrial posterior wall to the anterior aspect of the posterior aortic wall, aortic root (AR) from the anterior aspect of the posterior aortic wall to the anterior aspect of the anterior aortic wall, and main pulmonary artery (MPAp) from the anterior

Table 1 *Diagnoses of patients studied by suprasternal echocardiography*

	No. of patients
Normal	45
Pulmonary valve stenosis	20
Tetralogy of Fallot	20
Pulmonary atresia	18
Ventricular septal defect	
large	17
small	11
with pulmonary artery band	14
Atrial septal defect or persistent ductus arteriosus	6
Pulmonary vascular disease	10
Myocarditis/cardiomyopathy	8
Mitral valve disease	15
Pulmonary artery stenosis	3
Prematurity + PDA	10
Marfan's syndrome	4
Pectus excavatum	7
Truncus arteriosus (type 1)	3
Hypoplastic left heart syndrome	7
Tetralogy of Fallot with absent pulmonary valve	3
Aortic valve stenosis	17
Coarctation of aorta	13
d-transposition	19
l-malposition	9
Cor triatriatum	1
Total	280

Received for publication 29 January 1978

aspect of the posterior pulmonary artery wall to the anterior aspect of the anterior pulmonary artery wall.

Suprasternal echocardiography was performed using the special suprasternal transducer (Aerotech) 2·25 or 5 MHz 6 mm diameter on the suprasternal notch, angled inferiorly and slightly posteriorly to record the aortic arch (AA), right pulmonary artery (RPA), and left atrium (LAss) in its superoinferior axis. Whenever possible left atrial measurements were made immediately posterior to the mitral annulus. At this point left atrial contraction could be observed following the P wave of the surface electrocardiogram; this recording was possible in most infants and young children, though in older children and adults the mitral annulus often could not be detected and the left atrial inferior wall was recorded as a flat immobile structure.

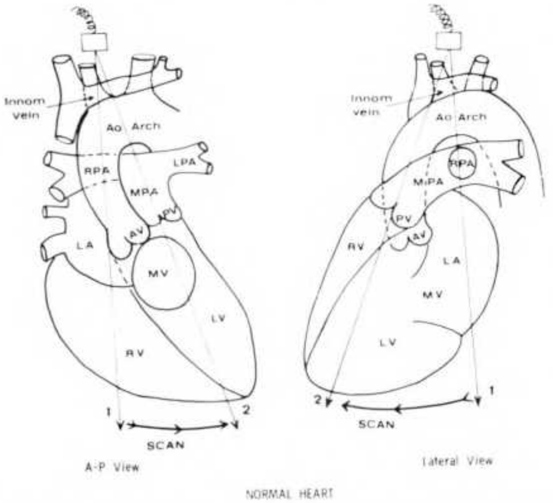


Fig. 1 (a) *Diagram of normal heart in anteroposterior and lateral views showing the ultrasound path in routine scan from position 1 to position 2 or vice versa.*

From this point of reference a routine scan was made by tilting the transducer leftward and anteriorly to obtain a continuous scan from the right pulmonary artery to the main pulmonary artery and valve where feasible; as this was done, the aortic arch progressively gave way to the superiorly placed main pulmonary artery. Alternatively, scans could be made in the reverse direction from the main pulmonary artery to the right pulmonary artery (Fig. 1). Contrast echocardiography was performed to confirm the identification of the structures mentioned, namely right pulmonary artery, aortic arch, left atrium, and main pulmonary artery.

In premature infants with the respiratory distress syndrome it was difficult to obtain a continuous scan from the right pulmonary artery to the main pulmonary artery. The origin of the left pulmonary artery could occasionally be located by scanning from the main pulmonary artery directly posteriorly. An echo-free space was sometimes noted superior to the aortic arch in infants, or superior to the main pulmonary artery in older children and contrast echocardiography confirmed that this space was the innominate vein. The oesophagus could at times be identified inferior and posterior to the left atrium when the patient swallowed saliva

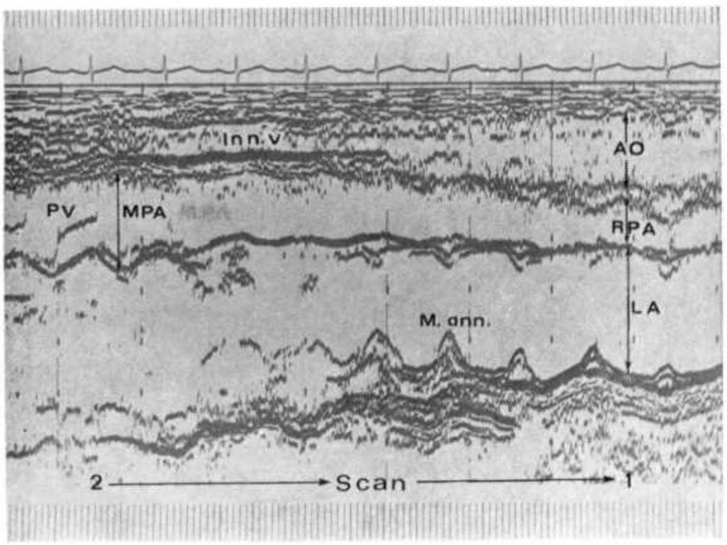


Fig. 1 (b) *Echocardiographic scan from position 2 to position 1.*
Ao arch, aortic arch;
AV, aortic valve;
Inn. v, innominate vein;
LA, left atrium;
LV, left ventricle;
M. ann, mitral annulus;
MPA, main pulmonary artery;
MV, mitral valve;
PV, pulmonary valve;
RPA, right pulmonary artery;
RV, right ventricle.

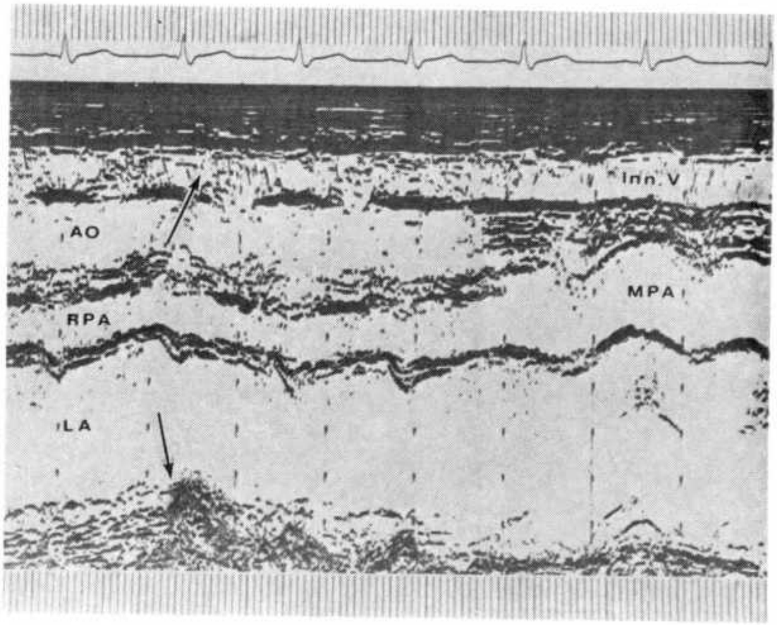


Fig. 2 *Scan from RPA to MPA in child with coarctation. Top arrow indicates innominate vein faintly opacified by contrast saline injected from intravenous line in left upper limb vein. Lower arrow indicates oesophagus lying inferior to left atrium, opacified by microbubbles in swallowed saliva.*

containing micro-bubbles (Fig. 2). The aortic valve could occasionally be located inferior and medial to the main pulmonary artery by scanning more medially than usual (Fig. 3). In certain patients the size and position of the distal aortic arch could be ascertained by scanning posteriorly leftward or rightward from the reference position. Other scanning procedures for malposition complexes will be described in a later section.

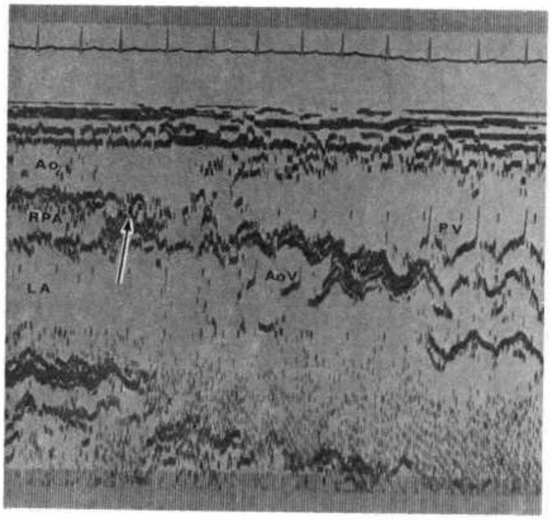


Fig. 3 *Scan from child with ventricular septal defect and pulmonary artery band. Arrow indicates pulmonary artery band at origin of right pulmonary artery. The transducer had been tilted more medially than usual to record aortic valve lying medial and inferior to main pulmonary artery and pulmonary valve.*

Measurements of the aortic arch, right pulmonary artery, left atrium, and main pulmonary artery were made in end-systole, as shown in Fig. 1. Measurements of the aortic arch, right pulmonary artery, left atrium, and main pulmonary artery were also made from cineangiocardiograms by comparison with catheter diameter in 15 patients who underwent cardiac catheterisation, and were compared with echocardiographic measurements made within 48 hours of the catheterisation. Praecordial and suprasternal measurements of the various structures were compared and ratios, regression curves and equations, and correlation coefficients obtained. Serial echocardiographic measurements were made in 20 patients.

Results

MEASUREMENTS OF AORTA, PULMONARY ARTERY, AND LEFT ATRIUM

Echocardiographic (X_1) and angiographic (Y_1) measurements of the great vessels and left atrium showed good correlation ($R=0{\cdot}85$; $Y_1=-0{\cdot}01+1{\cdot}06\ X_1$). There was more variation with left atrial measurements than with measurements of aorta and pulmonary artery.

Measurements of the aorta made suprasternally

(X_2) and praecordially (Y_2) were generally similar (R=0·88; Y_2=0·05+0·99 X_2; AA/AR=1·03±0·19). Patients with significant aortic valve stenosis had a tendency to larger AA/AR ratios resulting from post-stenotic dilatation of the aortic arch and small aortic annulus.

Praecordial measurements of main pulmonary artery (X_3) were generally slightly larger than suprasternal measurements (Y_3) (MPAss/MPAp=0·93±0·16; R=0·74; Y_3=0·59+0·68 X_3). There was wider scatter and variation in measurements of the main pulmonary artery, which is probably explained by the obliquity of the main pulmonary artery and the difficulty of obtaining accurate praecordial measurements of its diameter; measurement of a portion of the right ventricular outflow tract was usually included. Only in patients with a large main pulmonary artery in whom recording of two pulmonary valve leaflets was obtained was it possible to obtain a more accurate measurement of the true dimension of the main pulmonary artery. Suprasternal measurements of the proximal main pulmonary artery may at times be difficult because of the obliquity of the scan as well as the obliquity of the main pulmonary artery. However, suprasternal measurements of the distal main pulmonary artery may give a more accurate assessment of the size of the vessel at that site.

Suprasternal measurements of the left atrium (X_4) were consistently larger than praecordial measurements (Y_4) (LAss/LAp=1·53±0·29; R=0·88; Y_4=0·05+0·64 X_4) though the ratio varied. In only two out of three patients with tetralogy of Fallot with absent pulmonary valve was the suprasternal left atrial measurement smaller than the praecordial measurement; this resulted from compression of the left atrium superoinferiorly by the aneurysmal rightpul monary artery (Fig. 4C).

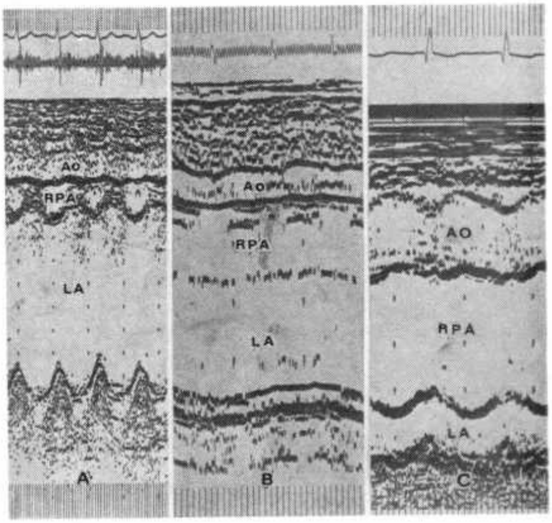


Fig. 4 *Miscellaneous suprasternal echocardiograms.* (A) *Severe mitral regurgitation with large left atrium.* (B) *Hypoplastic left heart syndrome with small aortic arch, but dilated right pulmonary artery and left atrium.* (C) *Tetralogy of Fallot with absent pulmonary valve showing aneurysmal right pulmonary artery compressing left atrium superoinferiorly and also dilated aortic arch.*

Table 2 *Suprasternal echocardiographic measurements*

Classification	*No. of patients*	*LAss/LAp*	*AA/RPA*	*LA/AA*	*AA/MPA*
Normal	45	1·59 ±0·21	1·46 ±0·23	1·49 ±0·26	1·03 ±0·16
Pulmonary valve stenosis	20	1·45 ±0·26	1·16 ±0·22	1·40 ±0·27	0·89 ±0·14
Tetralogy of Fallot	20	1·58 ±0·32	1·75 ±0·44	1·30 ±0·29	1·12 ±0·32
Pulmonary atresia	18	1·50 ±0·41	2·64 ±0·93	1·21 ±0·25	2·00 ±0·69
VSD large	17	1·68 ±0·30	1·22 ±0·19	1·95 ±0·42	0·77 ±0·12
small	11	1·54 ±0·23	1·53 ±0·32	1·52 ±0·28	1·01 ±0·21
with PA band	14	1·61 ±0·26	1·23 ±0·34	1·79 ±0·46	0·78 ±0·19
ASD or PDA	6	1·48 ±0·08	1·16 ±0·15	1·61 ±0·30	0·75 ±0·16
Pulmonary vascular disease	10	1·58 ±0·30	1·26 ±0·28	1·72 ±0·62	0·80 ±0·20
Myocarditis/cardiomyopathy	8	1·44 ±0·18	1·41 ±0·31	2·08 ±0·35	0·99 ±0·10
Mitral valve disease	15	1·42 ±0·26	1·34 ±0·17	2·37 ±0·57	0·85 ±0·15
Pulmonary artery stenosis	3	1·93 ±0·67	1·80 ±0·38	1·64 ±0·54	—
Prematurity + PDA	10	1·71 ±0·23	1·44 ±0·31	1·55 ±0·27* 1·94 ±0·31†	—
Marfan's syndrome	4	1·98 ±0·67	1·81 ±0·40	1·33 ±0·49	1·26 ±0·21
Pectus excavatum	7	2·27 ±0·50	1·43 ±0·28	1·71 ±0·37	0·99 ±0·16
Hypoplastic left heart syndrome	7	1·53 ±0·65	0·63 ±0·39	3·51 ±1·62	0·46 ±0·26
Tetralogy of Fallot and absent pulmonary valve	3	0·82 ±0·38	0·70 ±0·16	0·79 ±0·27	—
Aortic valve stenosis	17	1·44 ±0·32	1·67 ±0·38	1·39 ±0·32	1·21 ±0·31
d-transposition	19	1·80 ±0·60	0·97 ±0·12	1·60 ±0·30	—
Coarctation of aorta	13	1·71 ±0·37	1·27 ±0·33	1·41 ±0.11* 1·87 ±0·09†	1·03 ±0·29
Truncus arteriosus with pulmonary artery band	3	1·93 ±0·52	2·17 ±0·43	1·23* 1·78 ±0·07†	

* Without heart failure. † With heart failure.

AA/RPA RATIO (Table 2)
In 35 normal subjects the ratio was 1·46 ±0·23. It was significantly increased in patients with pulmonary atresia, tetralogy of Fallot, pulmonary artery stenosis, Marfan's syndrome, and slightly increased in aortic valve stenosis. This was the result of enlargement of the aortic arch and small right pulmonary artery in the first three conditions mentioned, and enlargement of the aortic arch in the other two. The ratio was significantly smaller in patients with hypoplastic left heart syndrome (Fig. 4B), significant left-to-right shunt, pulmonary hypertension from a variety of causes, tetralogy of Fallot with absent pulmonary valve, pulmonary valve stenosis, and d-transposition of the great arteries. In hypoplastic left heart syndrome this was the result of the hypoplastic aortic arch and dilatation of the right pulmonary artery. In the other conditions the change was the result of enlargement of the right pulmonary artery from a variety of causes. In patients with ventricular septal defect there was a difference between patients with small defects and those with larger defects or who had required pulmonary artery banding. In one patient with a ventriculoatrial shunt for hydrocephalus, a significantly smaller AA/RPA ratio suggested pulmonary hypertension and prompted further investigation of the patient who subsequently underwent revision of his shunt.

AA/MPASS RATIO (Table 2)
In normal patients the ratio was 1·03 ±0·16. In the various cardiac malformations the changes were generally similar to those observed for AA/RPA ratio.

LASS/AA RATIO (Table 2)
In normal patients the ratio was 1·49 ±0·26. The ratio was significantly increased in patients with mitral valve disease (Fig. 4A), cardiac failure resulting from truncus, coarctation, myocarditis, or cardiomyopathy, large ventricular septal defect, and persistent ductus arteriosus. This was related to enlargement of the left atrium. The ratio was also increased in patients with pectus excavatum as a result of anteroposterior compression of the left atrium, and in patients with the hypoplastic left heart syndrome as a result of the small aortic arch and enlargement of the left atrium. The ratio was decreased in patients with pulmonary atresia, tetralogy of Fallot, and Marfan's syndrome mainly as a result of enlargement of the aortic arch. The ratio was also decreased in tetralogy of Fallot with absent pulmonary valve, as a result of enlargement of the aortic arch and compression of the left atrium by the aneurysmal right pulmonary artery.

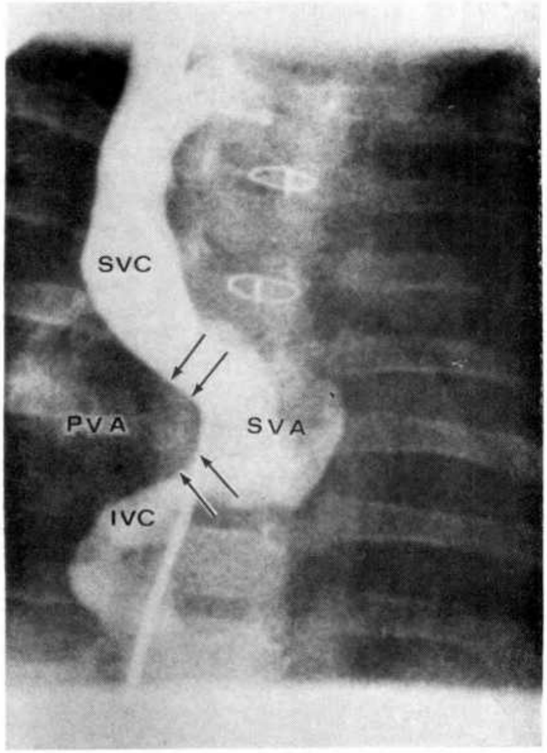
OTHER OBSERVATIONS
The pulmonary, aortic, and mitral valves were commonly detected in infants. In older children the pulmonary valve was more easily detected in pulmonary valve stenosis and pulmonary hypertension, the aortic valve in aortic valve stenosis and in pulmonary atresia, and the mitral valve in atrioventricular canal. This may supplement information on the valves obtained by praecordial echocardiography.

Structures within the atrial cavity were also detected. The atrial baffle was detected in five children after Mustard's operation for d-transposition of the great arteries. A rightward transverse scan from the systemic venous atrium often showed the superior and inferior aspects of the baffle which divided the cavity into three chambers. Contrast echocardiography confirmed the superior cavity as the superior vena caval inflow, the middle cavity as the pulmonary venous atrium, and the inferior cavity as the inferior vena caval inflow. It was often difficult to get a good view of the inferior vena caval inflow (Fig. 5a, b). In a patient with cor triatriatum, the membrane was seen as a single or double linear shadow across the atrial cavity. In the latter instance the superior and inferior aspects of the bulging membrane had been caught by the transducer beam; these linear shadows disappeared after successful operation (Fig. 5c).

SCANNING TECHNIQUES IN ABNORMALITIES OF PULMONARY ARTERY AND AORTA
Routine scans from the right pulmonary artery to the main pulmonary artery (MPA) made it possible to assess the size and integrity of both vessels.

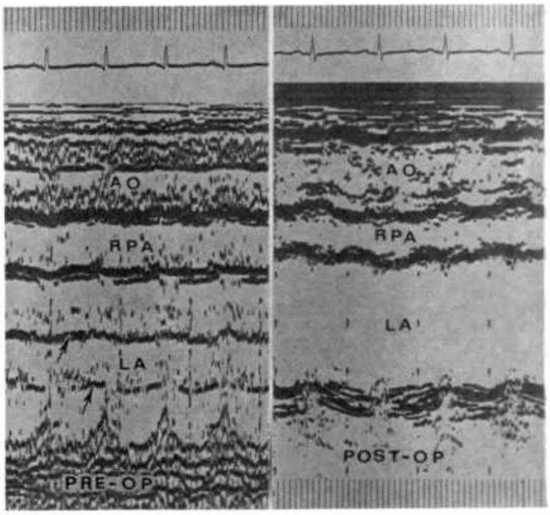
In 18 patients with pulmonary atresia, the hypoplastic right pulmonary artery could be identified but in 11 it was not possible to detect continuity with a hypoplastic main pulmonary artery (Fig. 6a). These observations were in close agreement with angiocardiographic and surgical findings. The method thus appears to be a specific and sensitive technique to assess the presence or absence of the main pulmonary artery.

Four patients with a pulmonary artery band (PAB) had both preoperative and postoperative suprasternal echocardiography. The site and efficacy of the banding could be assessed by reference to the constricted lumen of the main pulmonary artery at the site of the band (Fig. 6b). Echocardiographic (X) and angiographic (Y) measurements of the banded pulmonary artery in 12 patients showed good correlation ($Y=0{\cdot}24+0{\cdot}54X$; $R=0{\cdot}86$). Two patients who had tight pulmonary artery bands required surgical revision; subsequent echocardiographic assessment showed larger dimensions. Three other patients had serial echocardiographic measurements over a period of six months showing constancy of pulmonary artery band size. Two other patients had distal migration of the band to



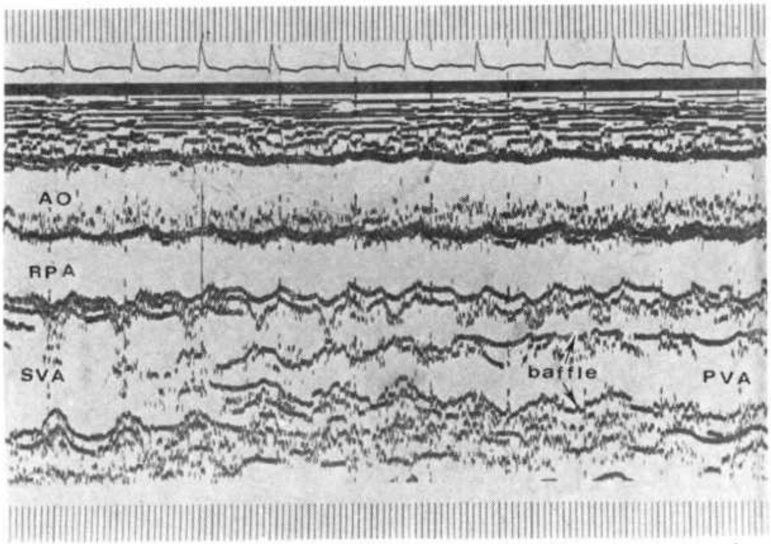
a

Fig. 5 (a) *Superior vena caval angiogram after Mustard procedure for d-transposition (anteroposterior view). Arrows point to atrial baffle. IVC, inferior vena cava; PVA, pulmonary venous atrium; SVA, systemic venous atrium; SVC, superior vena cava.*



c

Fig. 5 (c) *Suprasternal echocardiogram in child with cor triatriatum.* (left) *Preoperative, showing dilated left atrium with two linear shadows* (shown by arrows) *lying within the cavity, and dilated right pulmonary artery.* (right) *Postoperative, showing disappearance of linear shadows within the normal-sized left atrium; right pulmonary artery has also diminished in size.*



b

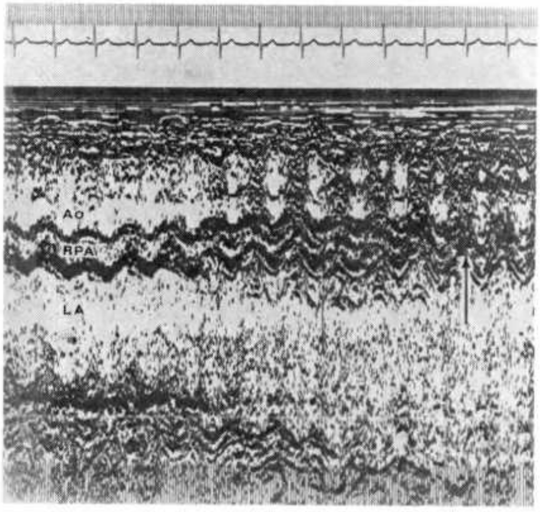
Fig. 5 (b) *Transverse and rightward echocardiographic scan from SVA to PVA. The atrial baffle has divided the chamber into three portions; superior SVC inflow, middle PVA, inferior IVC inflow.*

the bifurcation of the main pulmonary artery, with partial occlusion of the origin of the right pulmonary artery (Fig. 3). One other patient had a loose band. Banding was thought to be effective if the ratio PAB/MPA was between 0·35 and 0·6, tight if PAB/MPA ratio was less than 0·35, and loose if the ratio was greater than 0·6.

In three out of six patients with tetralogy of Fallot who required a Waterston anastomosis, echocardiography showed a right pulmonary artery stenosis at the anastomotic site. Stenosis of the right pulmonary artery at its origin was shown in four patients (Fig. 6c) and supravalvar pulmonary artery stenosis in one patient with tetralogy of Fallot. Aneurysmal dilatation of the main pulmonary artery after correction of Fallot's tetralogy with outflow patch was documented in three patients.

In one hydrocephalic patient with a broken ventriculoatrial shunt, the metal tip of which was lodged in the distal right pulmonary artery, it was possible by appropriate scanning to follow the proximal radiolucent tubing from the right pulmonary artery to the main pulmonary artery and thence to the left pulmonary artery.

Scans from proximal to distal aortic arch were made in patients with tetralogy of Fallot, pulmonary atresia, aortic valve stenosis, complex cyanotic heart disease, and coarctation of the aorta. The distal aortic arch was usually of the same size as or slightly smaller than the proximal aortic arch. Out of 14 patients with coarctation of the aorta, distal isthmic



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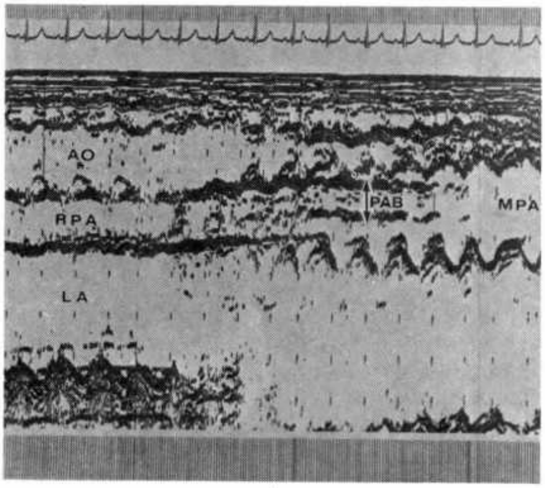

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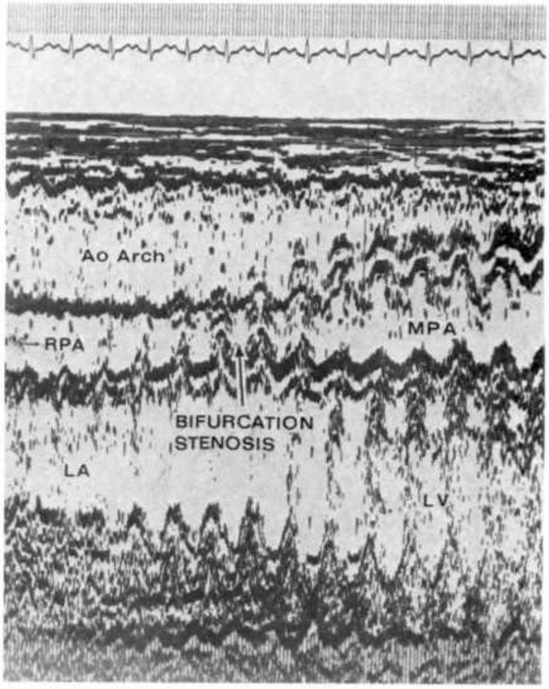
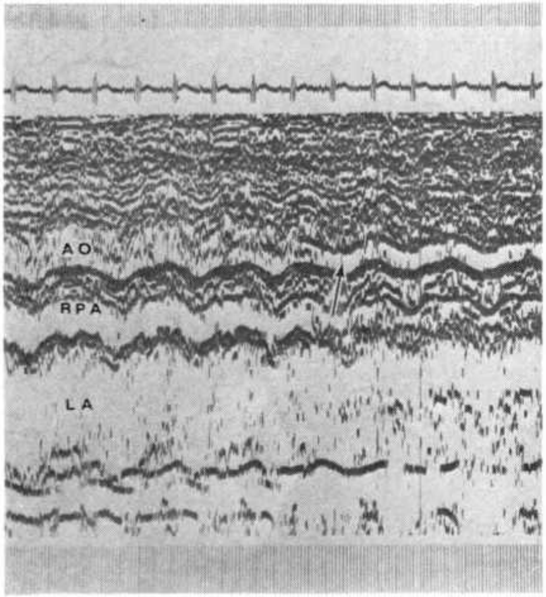


Fig. 6 *Scans from right pulmonary artery to main pulmonary artery.* (a) *Pulmonary atresia with absent main pulmonary artery: dilated aortic arch and hypoplastic right pulmonary artery; no main pulmonary artery is seen* (arrow). (b) *Effective pulmonary artery band (PAB) lying away from origin of right pulmonary artery and in distal half of main pulmonary artery.* (c) *Right pulmonary artery stenosis at bifurcation in tetralogy of Fallot.*

hypoplasia was documented in five patients. This was in close agreement with angiographic findings (Fig. 7a). Six patients with tetralogy of Fallot had a right-sided aortic arch suggested by echocardiography and confirmed on angiography. The course of an l-malposed aorta crossing the mediastinum and descending as a right-sided arch was correctly predicted before cardiac catheterisation in a neonate with single ventricle and pulmonary atresia. Recently in three patients with persistent ductus arteriosus (two with transposition of the great arteries) the pulmonary aspect of the persistent ductus was visualised as an echo-free space inferior to the distal aortic arch and separated from the left pulmonary artery (Fig. 7b, c). This space disappeared after ligation of the ductus in two patients and spontaneous closure in one. An alternative way of detecting the ductus was by scanning from the main pulmonary artery directly posterior to the distal aortic arch and showing continuity between the main pulmonary artery and the echo-free space beneath the distal arch; it appears that this method is only possible when a ductus is long and tubular with distinct demarcation from the left pulmonary artery.



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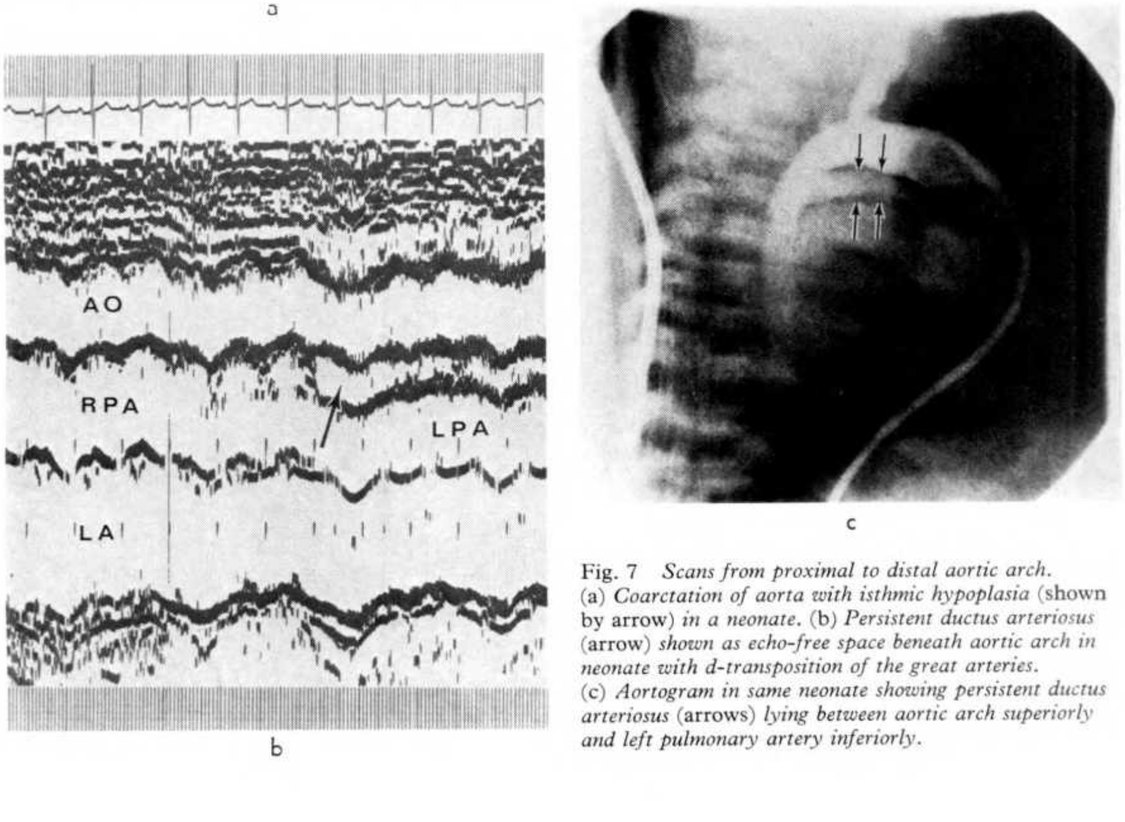

b

c

Fig. 7 *Scans from proximal to distal aortic arch.* (a) *Coarctation of aorta with isthmic hypoplasia* (shown by arrow) *in a neonate.* (b) *Persistent ductus arteriosus* (arrow) *shown as echo-free space beneath aortic arch in neonate with d-transposition of the great arteries.* (c) *Aortogram in same neonate showing persistent ductus arteriosus* (arrows) *lying between aortic arch superiorly and left pulmonary artery inferiorly.*

SCANNING TECHNIQUES IN MALPOSITION COMPLEXES

From the reference position scans were made by tilting the transducer anteriorly and leftward, centrally, or rightward to document the following: (a) continuity of the aortic arch with the ascending aorta and aortic valve where possible; (b) continuity of the right pulmonary artery with the main pulmonary artery and pulmonary valve where possible; and (c) the relative positions of the ascending aorta and the main pulmonary artery and, where possible, of the aortic valve and the pulmonary valve. Occasionally, when only one vessel could be detected superior to the left atrium, from the reference position it was necessary to scan transversely to locate the other vessel, usually the aortic arch; this was observed in patients with l-malposition in whom the aortic arch usually lay superior and to the left of the right pulmonary artery (Fig. 8). Occasionally in patients with right-sided aortic arch, the arch lay more to the right than usual. This transverse scan was also of value in the detection of the right pulmonary artery in patients with pulmonary atresia. In scanning anteriorly, it was often necessary to place the transducer more anteriorly and superficially on the sternal notch to obtain a good continuous scan.

In normal patients scans from the right pulmonary artery to the main pulmonary artery were obtained as described above. Some difficulty was experienced with premature infants with respiratory distress syndrome. The detection of a semilunar valve just inferior to the main pulmonary artery taken in conjunction with the praecordial echocardiographic findings confirmed normal orientation of the vessels. Scanning from the aortic arch to the ascending aorta and aortic valve was not possible in normal subjects.

In d-transposition of the great arteries the aortic arch and right pulmonary artery were normally related. However, routine scanning anteriorly and leftward from the right pulmonary artery failed to record continuity with the main pulmonary artery when the aortic arch was no longer seen on the scan. This was a good indication of the diagnosis. The main pulmonary artery could only be recorded in a more medial, inferior, and posterior postion at the point on the scan when the aortic arch was still lying superior to it (Fig. 9a). Aortic arch to ascending aorta continuity could be shown by scanning anteriorly, centrally, or rightward. This was possible (though difficult) in all infants with d-transposition but was much more difficult in older patients. The anteriorly and superiorly placed aortic valve was located in two patients and an aortic valve to pulmonary valve scan was successfully accomplished in these two patients.

In l-malposition complexes, the aortic arch was usually superior to the left pulmonary artery and

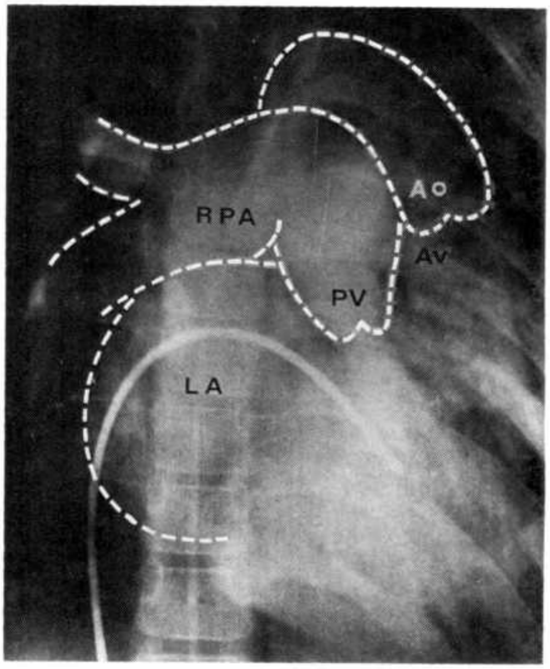

Fig. 8 (a) *Angiocardiogram in child with l-malposition, single ventricle, and pulmonary stenosis, showing leftward position of aortic arch relative to right pulmonary artery.*

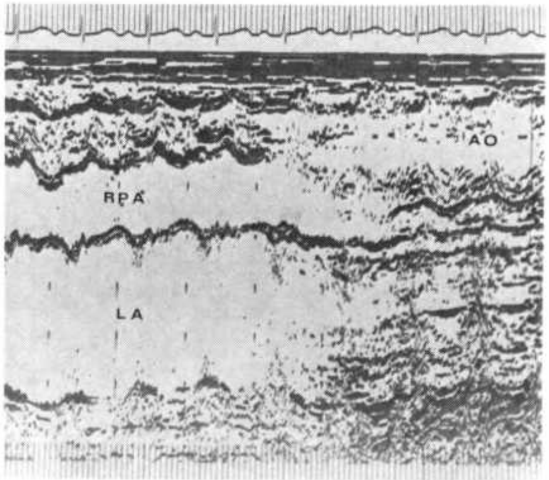

Fig. 8 (b) *Suprasternal echocardiogram in another child with l-malposition. Transverse and leftward scan locates aortic arch.*

therefore to the left of the right pulmonary artery. Aortic arch to ascending aorta continuity could be shown in seven patients by scanning anteriorly and leftward. The anterior, superior, and leftward aortic valve was located in two neonates (Fig. 9b). The main pulmonary artery was recorded as in d-transposition in a medial, inferior, and posterior position, but in these patients the aortic arch was not recorded superiorly at the same time. The pulmonary valve was located in two patients.

Discussion

Suprasternal echocardiography as described previously has a useful though limited role, but the introduction of the scanning techniques described above has broadened its application. New information is available regarding structures like the right pulmonary artery, proximal and distal aortic arch, and main pulmonary artery. Scans from the right pulmonary artery to the main pulmonary artery make it possible to assess the size and integrity of both vessels. This has been shown in cases of pulmonary atresia, tetralogy of Fallot, right pulmonary artery stenosis, Waterston anastomosis, pulmonary artery banding, supravalvar pulmonary stenosis, and pulmonary artery aneurysm. The information provided is of importance for planning surgical treatment in patients with pulmonary atresia as well as in patients with a Waterston anastomosis. The effectiveness of pulmonary artery banding has been assessed by direct visualisation of the site and size of the lumen of the band. Scans from the proximal to the distal aortic arch make it possible to assess integrity, size, and position of the whole aortic arch. Isthmic hypoplasia and persistent ductus arteriosus have been shown, and right and left aortic arch distinguished.

In transposition and malposition complexes, suprasternal scanning procedures, in conjunction with praecordial echocardiography, have made possible proper identification of semilunar valves and roots of great arteries. Usually the aortic arch is superior to the right pulmonary artery and is continuous with the ascending aorta and aortic valve on appropriate scans. In the neonate, care must be taken, however, to differentiate the innominate vein which is occasionally detected above the aortic arch. In most patients with l-malposition the aortic arch lies above and to the left of the right pulmonary. In some patients with right aortic arch the arch may lie much more to the right than in others.

The right pulmonary artery lies inferior to the aortic arch and is continuous with the main pulmonary artery and pulmonary valve on appropriate scans. Comparison of the relative positions of the roots of the great arteries on suprasternal and praecordial echocardiograms make it possible to identify the arteries and semilunar valves. This non-invasive method of diagnosis of malposition complexes has proved to be useful and could also help in the diagnosis of the rare s-d-l transposition (atrial situs solitus, d-ventricular loop, l-arterial loop) and posterior transposition complexes. This method is superior to the contrast suprasternal technique described by Mortera *et al.*[4] because it is non-invasive and is suitable for all cases of mal-

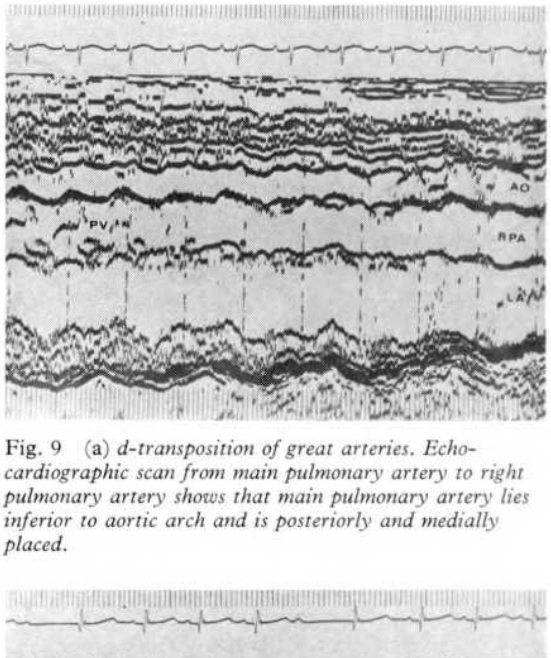

Fig. 9 (a) *d-transposition of great arteries. Echocardiographic scan from main pulmonary artery to right pulmonary artery shows that main pulmonary artery lies inferior to aortic arch and is posteriorly and medially placed.*

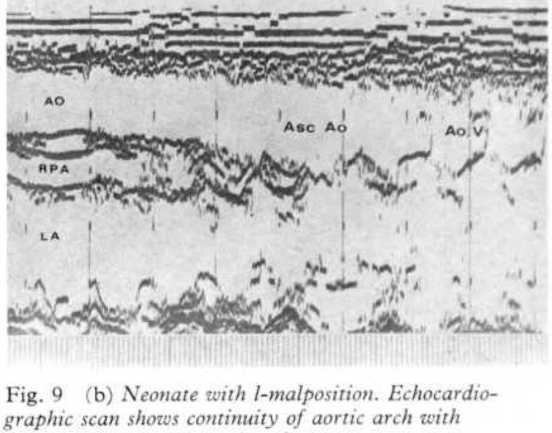

Fig. 9 (b) *Neonate with l-malposition. Echocardiographic scan shows continuity of aortic arch with ascending aorta and aortic valve.*

position, whereas the latter method requires invasive contrast studies and is of limited use for patients with d-transposition of the great arteries with ventricular septal defect or single ventricle, and those patients with persistence of fetal circulation with gross right-to-left atrial shunting.

Angiocardiographic and echocardiographic measurements of great arteries show good correlation. There is more variation with left atrial measurements apparently because angiocardiographic and echocardiographic techniques measure different diameters of a three-dimensional structure. The introduction of scanning procedures may perhaps enable some standardisation of the technique for obtaining left atrial measurements. The largest left atrial diameter is just behind the mitral annulus and measurements should be made here when possible. Consistent values are obtained when serial measurements are made.

Biaxial measurements of left atrial dimension in this study show a consistently larger suprasternal measurement than reported by Allen *et al.*[3]. These differences were greater in patients with antero-posterior compression of the left atrium from pectus excavatum and in premature infants with sternal retraction associated with the respiratory distress syndrome or persistent ductus. In only two patients, with tetralogy of Fallot with absent pulmonary valve and aneurysmal dilatation of the right pulmonary artery was the suprasternal left atrial measurement smaller than the praecordial. These results are what would be expected from the ellipsoidal shape of the left atrium on lateral view angiocardiograms. On the other hand, Allen *et al.*[3] reported equal suprasternal and praecordial echocardiographic dimensions.

Biaxial visualisation of left atrial myxomas has been described[2]. This technique has also been used to locate the atrial baffle after the Mustard operation for d-transposition of the great arteries. The incorporation of a transverse scan makes it possible to assess the superior vena caval and perhaps inferior vena caval inflow into the systemic venous atrium. The atrial membrane of cor triatriatum was also identified in this manner in one patient.

In conclusion, the introduction of scanning procedures has been shown to enhance significantly the usefulness of suprasternal echocardiography. Scanning suprasternal echocardiography should, therefore, form a part of the routine echocardiographic assessment of the child with heart disease.

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Addendum. Since the submission of this paper for publication, we have studied three patients with complete aortic arch interruption. In all three patients we have failed to demonstrate an aortic arch using the scanning procedures described. In one of these patients, a neonate, suprasternal echocardiography appeared to show an echo-free space superior to the right pulmonary artery, but scanning showed this to result from a grossly dilated main pulmonary trunk.

Br Heart J 1980; **43**: 159–163

Diastolic movement of mitral valve in hypertrophic cardiomyopathy

An echocardiographic study[*]

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SUMMARY Diastolic movement of the mitral valve and its relation to various aspects of left ventricular anatomy and function has been investigated in 15 patients with hypertrophic cardiomyopathy. Echocardiograms showing left ventricular cavity and mitral valve simultaneously were recorded and subsequently digitised in order to obtain continuous plots of left ventricular dimension, its rate of change, and peak diastolic closure rate of the anterior leaflet of the mitral valve. Septal and posterior wall thicknesses, together with left ventricular cavity and outflow tract dimension in mid-systole, were also measured directly on the echocardiograms. All the measurements were compared with those in 14 normal subjects. Patients with hypertrophic cardiomyopathy had smaller ventricles, with a conspicuous increase in septal thickness compared with those of normal subjects. Posterior wall thickness was only slightly increased, rapid filling period was normal, whereas both the peak rate of increase of left ventricular dimension and the peak mitral diastolic closure rate were low. However, no relation between these two indices was found. Instead, mitral valve closing velocity was strongly correlated with left ventricular outflow tract dimension. This relation was further validated by the infusion of isoprenaline, resulting in a simultaneous reduction of left ventricular outflow tract dimension and peak mitral closing velocity.

In patients with hypertrophic cardiomyopathy it is concluded that anatomical changes of the left ventricular outflow tract are responsible for a disruption of the normal pattern of flow behind the anterior leaflet of the mitral valve, which results in a diminished closure rate of the valve in diastole.

Slow diastolic closure rate of the anterior leaflet of the mitral valve is a common finding in patients with hypertrophic cardiomyopathy. It has been related to a reduction in left ventricular diastolic compliance[1 2] which usually results in diminished transmitral flow.[3]

However, angiographic studies in hypertrophic cardiomyopathy[4 5] have shown that filling rates of the left ventricle can be within normal limits, whereas the filling pattern may be abnormal.[6] Subsequently, abnormal relaxation of the left ventricle was confirmed by echocardiography.[7]

An echocardiographic study was undertaken in a group of patients with hypertrophic cardiomyopathy in an attempt to gain further information about the relation between the diastolic closure rate of the mitral valve and left ventricular filling. In addition, left ventricular anatomical changes were investigated to assess their connection with mitral valve motion in diastole.

Subjects and methods

Fifteen patients (12 men and three women, age range 18 to 54 years, mean 36 years) with hypertrophic cardiomyopathy were studied. In all the patients the diagnosis was based on angiographic criteria.[8] All the patients were in sinus rhythm at the time of the study; nine of them were taking beta-blocking drugs.

For comparison, 14 normal subjects of similar ages were also studied.

Echocardiograms were obtained by means of an Ekoline 20A ultrasonoscope with a 2·25 MHz non-focused transducer, and a simultaneous electro-

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[*] Based on a paper presented at the Third European Congress on Ultrasonics in Medicine, Bologna, October 1978.

Received for publication 4 June 1979

cardiogram was recorded in all cases. Studies were made with the patients either supine or in a slightly left lateral position. The transducer was angled in order to obtain simultaneous recordings of the mitral valve, interventricular septum, and posterior left ventricular wall (Fig. 1). Measurements were made only when these echoes were clear and continuous throughout the cardiac cycle. In six patients, after informed consent, the tracings were repeated after an intravenous infusion of isoprenaline. The drug was injected as a single bolus of 3 to 5 μg over 15 seconds.

DIGITISING METHODS

Echocardiograms were digitised, as described by Gibson and Brown[9] using a Summagraphics digitising table, and subsequently processed by a Prime 300 computing system. Data points were generated for both sides of the interventricular septum, endocardium, and epicardium of the posterior wall and mitral valve leaflets, together with calibration signals representing 0·5 s and 1 cm, and the RR interval of the beat to be studied.

From the digitised data, plots were made of the position of the wall and mitral valve echoes, left ventricular dimension and its rate of change, and rate of change of mitral valve position. From these tracings (Fig. 2), the following measurements were made:

(1) Left ventricular dimension, measured directly at end-diastole, along with its peak rate of increase during diastole.
(2) Posterior wall and septal thicknesses, measured directly at end-diastole.
(3) Peak diastolic closure rate of the anterior leaflet of the mitral valve, taken from the curve of first differential of position.
(4) Rapid filling period, measured as the interval between the onset of forward movement of the

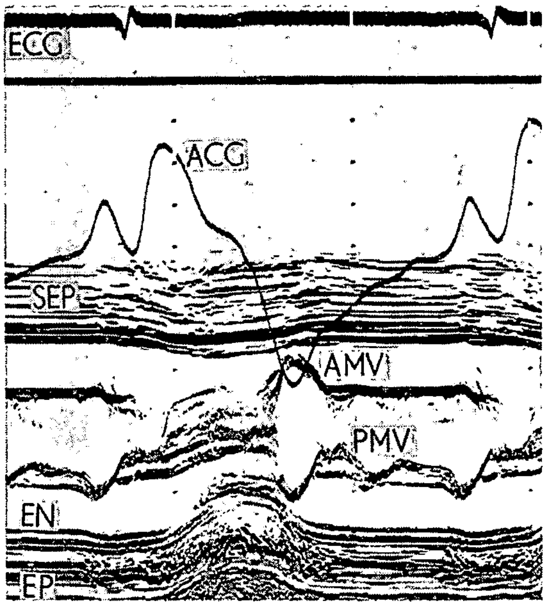

Fig. 1 *Echocardiogram of a patient with hypertrophic cardiomyopathy, showing septum, posterior wall, and mitral valve cusps. An apex cardiogram (ACG) is superimposed. AMV, anterior mitral valve leaflet; PMV, posterior mitral valve leaflet; EN and EP, endocardial and epicardial surfaces of the posterior left ventricular wall.*

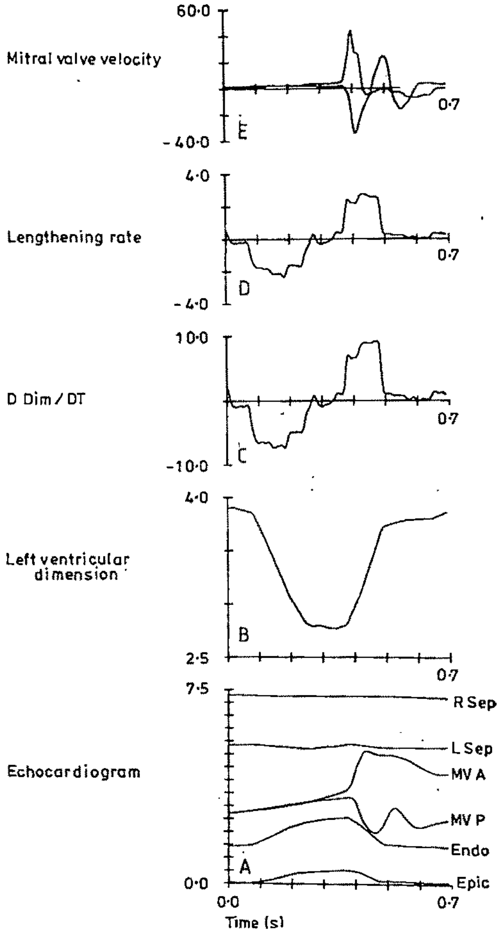

Fig. 2 *Computer output of the left ventricular cavity of a patient with hypertrophic cardiomyopathy, showing digitised echoes from the right (RSep) and left (LSep) side of the septum, endo- and epicardial (Epic) surfaces of the posterior wall, and mitral valve cusps. The left ventricular dimension curve* (above), *its rate of change (D Dim/DT), its normalised rate of change (lengthening rate), and mitral leaflet velocity* (top).

anterior mitral leaflet and the point at which the rate of increase of dimension had fallen to 20 per cent of its peak value[9].

(5) Dimension of the left ventricular outflow tract in mid-systole, taken as the minimum distance between the mitral valve apparatus and the left side of the septum. If systolic anterior movement of the mitral valve was present, the most anterior echo originating from the valve was used.

The comparison with the normal group was carried out using Student's t test.

Results

NORMAL SUBJECTS

Mean left ventricular cavity dimension at end-diastole was 4·7 ±0·5 cm, while septal and posterior wall thicknesses at the same time were 0·86 ±0·11 and 0·86 ±0·10 cm, respectively (Table). The peak rate of increase of dimension in diastole was 15·1 ± 4·4 cm/s, the duration of the rapid filling period was 148 ±29 ms, and the peak diastolic closure rate of the anterior mitral leaflet was 240 ±65 mm/s.

Table *Results of echocardiographic measurements in 14 normal subjects and 15 patients with hypertrophic cardiomyopathy*

	Normals	*Hypertrophic cardiomyopathy*	*P*
Diastolic dimension (cm)	4·7 ±0·5	3·8 ±0·6	<0·01
Septal thickness (cm)	0·86 ±0·11	1·92 ±0·39	<0·01
Post. wall thickness (cm)	0·86 ±0·10	1·17 ±0·17	<0·05
DDim/DT (cm/s)	15·1 ±4·4	7·6 ±3·2	<0·01
Rapid filling period (m/s)	148 ±29	157 ±42	n.s.
Peak closing rate of anterior mitral valve	240 ±65	96 ±51	<0·01

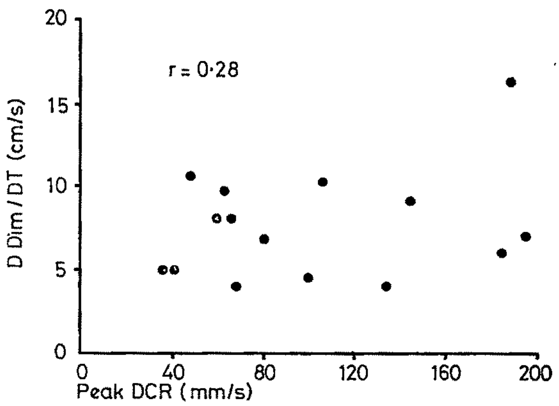

Fig. 3 *Relation between peak diastolic closure rate (DCR) of the anterior mitral leaflet and peak rate of increase in left ventricular dimension (D Dim/DT).*

PATIENTS WITH HYPERTROPHIC CARDIOMYOPATHY

Mean cavity dimension at end-diastole was 3·8 ± 0·6 cm, significantly smaller than normal (P < 0·01). Posterior wall thickness was only slightly increased (1·17 ±0·17 cm; P < 0·05), whereas septal thickness was greatly increased (1·92 ±0·39; P < 0·01).* Mean value of the rapid filling period was normal, with a wide scatter of values (157 ±42 ms). Both peak rates of dimension increase in diastole and diastolic closure of the mitral valve were low: 7·6 ±3·2 cm/s and 96 ±5 mm/s, respectively (P < 0·01). However, no relation was found between these two indices (Fig. 3). In addition, no relation was found between the peak diastolic closure rate of the mitral valve and the rapid filling period, the diastolic dimension of the left ventricle, or septal and posterior wall thicknesses. Instead, a strong correlation (r = 0·86) was found between peak mid-diastolic closure velocity of the mitral valve and left ventricular outflow tract dimension in mid-systole (Fig. 4).

In the six patients in whom isoprenaline was infused, the decrease in peak diastolic closure rate of the anterior leaflet of the mitral valve corresponded with the decrease in left ventricular outflow tract dimension, providing further validation of the relation between the two (Fig. 5). Peak diastolic closure rate of the posterior leaflet of the mitral valve remained unaffected by the drug infusion (Fig. 5). Isoprenaline was also injected in five

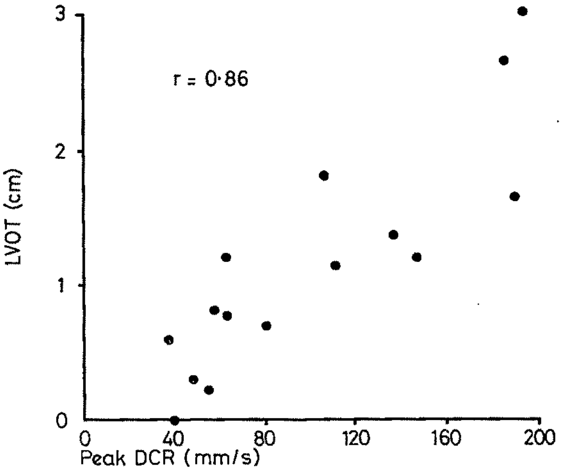

Fig. 4 *Relation between peak DCR of the anterior mitral leaflet and left ventricular outflow tract (LVOT) dimension at mid-systole.*

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*Significant systolic anterior movement of the mitral valve was present in seven patients.

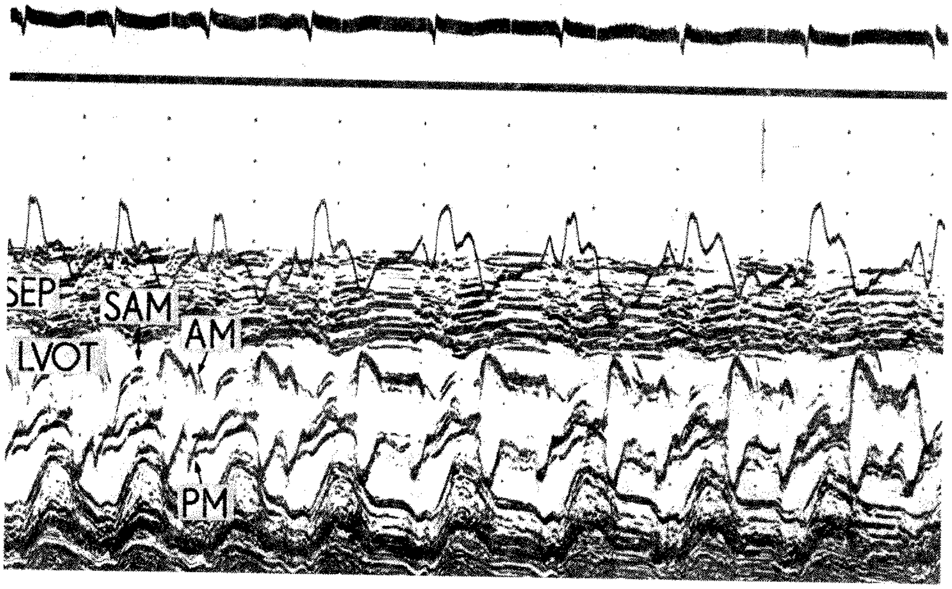

Fig. 5 *Echocardiogram of a patient with hypertrophic cardiomyopathy after the infusion of isoprenaline. The recording was taken when the effect of the drug was wearing off* (from left to right), *as shown by the decrease in heart rate. Together with the increase in left ventricular outflow tract (LVOT) dimension, a result of an almost complete disappearance of systolic anterior motion (SAM) of the anterior mitral cusp (AM), an increase of diastolic closing velocity of the latter is apparent. The movement of the posterior mitral cusp (PM) is unaffected by the drug.*

patients without echocardiographic evidence of hypertrophic cardiomyopathy and in none of them could we reproduce these findings.

Discussion

The significance of slow diastolic closure rate of the anterior leaflet of the mitral valve in patients with hypertrophic cardiomyopathy is still controversial. Reduction in left ventricular diastolic compliance,[1 2] diminished transmitral flow,[3] and slow ventricular filling[10] have been suggested as mechanisms of this reduction. However, the observation of normal movement of the posterior leaflet of the mitral valve with abnormal movement of the anterior one (Fig. 6) suggests that a local factor is interfering with mitral valve motion. This explains the asymmetrical behaviour of the valve.

In patients with hypertrophic cardiomyopathy, abnormal anatomical insertion of the anterior mitral valve leaflet[11] and abnormal angulation of the papillary muscles[12] could affect the diastolic movement of the valve in addition to contributing to the obstruction of the left ventricular outflow tract in systole.

In our study we have shown that a linear relation exists between left ventricular outflow tract dimension and peak diastolic closure rate of the mitral valve, whereas the latter is not related to any other anatomical or functional aspect of the left ventricle. Furthermore, when the dimension of the left ventricular outflow tract was acutely changed, using an inotropic drug such as isoprenaline, a concomitant decrease in peak diastolic closure rate of the anterior mitral valve was obtained. This is a further validation of the relation between the two indices.

It is difficult to explain how the anatomical changes of the left ventricular outflow tract interfere with the pattern of mitral valve motion in diastole. Bellhouse,[13] using a model mitral valve and left ventricle, has shown that when the ventricle is small a strong ring vortex is formed within the ventricle; this tends to close the valve in diastole. The vortex is asymmetrical, with its main strength concentrated behind the anterior cusp. This force which tends to close the valve can presumably be affected by the altered anatomy of the left ventricular outflow tract. If so the usual pressure would not be exerted on the anterior leaflet during mid-diastolic closure.

For this reason, in patients with hypertrophic cardiomyopathy we suggest that anatomical and functional abnormalities of both septum and mitral valve, which ultimately result in gross narrowing

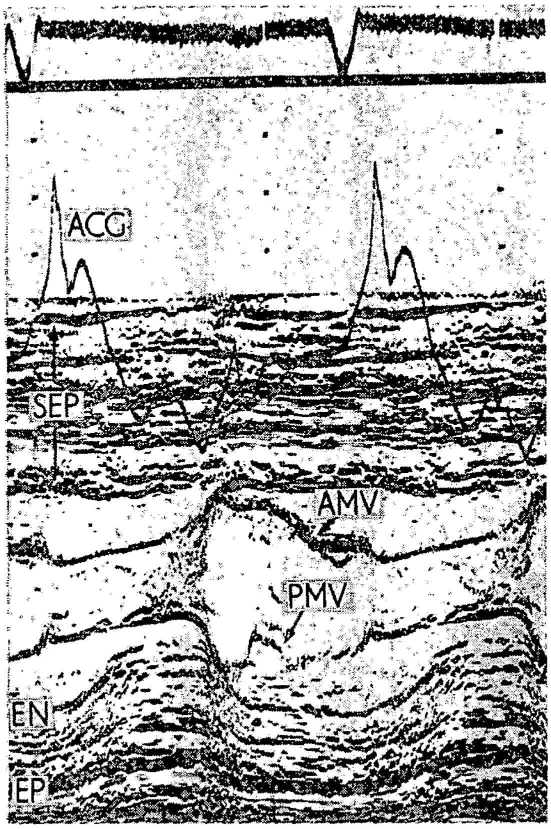

Fig. 6 *Echocardiogram of a patient with hypertrophic cardiomyopathy, showing left ventricular cavity and mitral valve leaflets. Slow mid-diastolic closure rate of the anterior cusp (AMV) is evident, whereas the posterior one (PMV) moves normally.*

of the left ventricular outflow tract, also interfere with the normal pattern of transmitral flow during diastole. This results in disruption of the ring vortex behind the anterior mitral leaflet and consequently in reduced mid-diastolic closure of the valve.

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Br Heart J 1980; **43**: 164–169

Natural history of left bundle-branch block*

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SUMMARY The purpose of this study was to examine factors associated with the development of complete left bundle-branch block and the prognosis in a group of people not in hospital, who had no clinical evidence of ischaemic or valvular heart disease. Twenty-nine cases of left bundle-branch block without clinical evidence of ischaemic heart disease were noted in the Manitoba cohort of 3983 men under observation since 1948. The most frequent electrocardiographic finding before development of left bundle-branch block was a normal electrocardiogram; left ventricular hypertrophy though infrequent, was the only abnormality significantly more common than in the rest of the group. The development of left bundle-branch block was associated with distinct leftward shift of the frontal plane mean QRS axis. The most frequent clinical cardiovascular event observed after development of the block was sudden death without previous clinical evidence of ischaemic heart disease. The five-year incidence of sudden death as the first manifestation of heart disease was 10 times greater in men with left bundle-branch block than in those without it.

Our knowledge of the natural history of complete left bundle-branch block has come almost entirely from patients in hospital with heart disease, because there are comparatively few data from apparently healthy populations. Because prognosis derived from clinical case studies may be inappropriate to the symptomless individual[1] prognostic data from persons without clinical evidence of heart disease are also necessary. Little is known about the electrocardiographic antecedents of left bundle-branch block and the electrocardiographic abnormalities that accompany its development, and there is still controversy about its association with changes in the mean frontal plane QRS vector.[2–4] We have examined data from the Manitoba study cohort of 3983 men (most of whom were between 25 and 34 years of age at entry in 1948) in order to assess these problems.

Methods

The details have been reported previously.[5 6] In summary, the study consists of 3983 men, who during World War II were either pilots or pilots in training in the Royal Canadian Air Force, or pilots licensed by the Department of Transport, and who at the time had a routine electrocardiogram in addition to the regular medical examination. After discharge from service, some continued to fly but most found different occupations and are in different strata of society. For each subject, the examination closest to 30 June 1948 (date population was defined) was selected as the entry examination. The mean age of the men was then 30·8 years. The age distribution was as follows: 318 men were between 15 and 24 years; 1479 were between 25 and 29 years; 1258 were between 30 and 34 years; 539 were between 35 and 39 years; 205 were between 40 and 44 years; 153 were between 45 and 54 years, and 31 were between 55 and 64 years. On the history, physical examination and electrocardiogram none had clinical manifestations of ischaemic heart disease at entry. Since then, they have been written to annually, with examinations and electrocardiograms at intervals of at first five years and later three years. The observation period was from 1 July 1948 until 30 June 1977, an average follow-up of 29 years. Annual contact has been lost with only one person.

DEFINITION AND CASE SELECTION

The electrocardiograms have been coded using rules for identification of deflections and measurement of intervals outlined by the American Heart Association committee on electrocardiography[7] and elabor-

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* Supported by a grant from the Department of National Health and Welfare, Ottawa, Canada, and Great Western Life Assurance Co.

Received for publication 17 August 1979

ated in the Minnesota code.[8] Descriptions of such variables as ST segment and T wave were those of the Minnesota code. The criteria used for the diagnosis of left bundle-branch block and other conduction disturbances were those outlined by the New York Heart Association[9] and the Minnesota code.[8] The mean frontal plane QRS vector was determined for each electrocardiogram, from the limb leads, using the hexaxial reference system,[7–10] calculated to the nearest 15° because this is a reasonable limit of precision of the method.[11]

Cases of left bundle-branch block included in the analysis satisfied the following criteria: detection of this conduction defect at a routine examination, and no clinical evidence of ischaemic or valvar heart disease on that examination or previously. Cases of left bundle-branch block associated with ischaemic heart disease were excluded.[12] Twenty-nine cases fulfilled the above criteria. The age distribution at the detection of left bundle-branch block was as follows: 35 to 39 years 3 men, 40 to 44 years 3 men, 45 to 49 years 4 men, 50 to 54 years 4 men, 55 to 59 years 8 men, 60 to 64 years 7 men. Left bundle-branch block developed during the observation period in all but one case, in whom it was present at entry; that case was only included for the analysis of prognosis.

Reports from doctors and hospitals, death certificates, information from relatives or executors of the estate and, whenever possible, necropsy findings were used to determine the cause of death. The definition of sudden death was that proposed by the World Health Organisation, namely natural death occurring immediately or within an estimated 24 hours after onset of symptoms.[13]

DATA ANALYSIS

The Wilcoxon matched pair test was used to test differences of paired observations. To test proportions, the χ^2 method was used. For analysis of prognosis, the life table method of Cutler and Ederer[14] was used because it has several advantages, including the calculation of cases lost to follow-up, a category that incorporates cases of death not resulting from ischaemic heart disease. Thus the survival rate pertaining if ischaemic heart were the only cause of death can be determined.

Results

FACTORS ASSOCIATED WITH DEVELOPMENT OF COMPLETE LEFT BUNDLE-BRANCH BLOCK

The most common electrocardiographic antecedent of left bundle-branch block was a normal electrocardiogram (Table 1). The next most frequent finding was left ventricular hypertrophy (satisfying Minnesota code voltage criteria 3–1 or 3–3 plus ST and T wave changes Minn. 4–1 to 4–3 and 5–1 to 5–3) in 14 per cent of cases. This was significantly ($P < 0{\cdot}05$) larger than the proportion of cases observed in the rest of the group without left bundle-branch block (14/100 versus 3·5/100). Pronounced left axis deviation or mean frontal plane QRS vector from −45° to −90° and incomplete left bundle-branch block seldom preceded the development of complete left bundle-bunch block. The proportion of ST segment and T wave abnormalities, pronounced left axis deviation, and prolonged PR interval in this group was not significantly different ($P > 0{\cdot}10$) from the proportion in the rest of the group without left bundle-branch block.

Table 1 *Electrocardiographic abnormalities before development of complete left bundle-branch block*

Abnormality		*Proportion*
None	15	(54%)
Left ventricular hyptertrophy*	4	(14%)
ST and T abnormalities†	4	(14%)
Pronounced left axis deviation‡	1	(3·5%)
Prolonged PR interval§	1	(3·5%)
Pronounced left axis deviation plus prolonged PR interval	1	(3·5%)
Incomplete left bundle-branch block¶	1	(3·5%)
Intraventricular conduction defect of indeterminant type**	1	(3·5%)
	28	

*Voltage criteria (Minn. 3–1 or 3–3[8],) plus ST and T abnormalities;
†ST and T abnormalities (Minnesota code 4-1 to 4-3, 5-1 to 3):
‡A QRS −45° to −90°[9];
§PR 0·22 (Minn. 6–3);
¶QRS duration 0·10 to 0·11 s with Â QRS + 75 to −75°[9]. There were no other cases with QRS duration 0·10 to 0·11 s;
**QRS duration 0·12 without QRS axis deviation or criteria for left or right bundle-branch block.

The development of left bundle-branch block was associated with the characteristic QRS, ST, and T wave changes. It was also associated with a significant ($P < 0{\cdot}001$) leftward shift in the mean frontal plane axis of QRS of −22·0 ± 5·5° (mean ± 1 SEM) from the last tracing (3·4 ± 0·2 years) before left bundle-branch block (Fig. 1). By comparison the *mean* change in frontal plane axis of QRS for the same ages in the entire group over the same time interval between electrocardiograms ranged from −3° to −7°. In contrast and not unexpectedly there was no significant change ($P > 0{\cdot}05$) in the PR interval from the tracing immediately before (PR = 16·2 ± 4 ms) to the electrocardiogram with the intraventricular conduction defect (PR 16·8 ± 4 ms).

PROGNOSIS OF LEFT BUNDLE-BRANCH BLOCK

The cardiovascular morbidity and mortality after the development of complete left bundle-branch block was: 17·2 per cent (5/29) had sudden death without prior cardiovascular symptoms; 3·4 per cent (1/29) developed angina pectoris and later died suddenly; 3·4 (1/29) had a cerebrovascular accident; none had myocardial infarction (an episode of chest pain associated with increases in blood levels of cardiac enzymes).

This experience is in distinct contrast to the rest of the population. The proportion of sudden deaths in men without clinical evidence of previous myocardial infarction is not only significantly larger ($P < 0{\cdot}01$), but also is over 10 times greater in the group with left bundle-branch block compared with those in the rest of the group without left bundle-branch block (20·7/100 versus 1·6/100).

To focus on sudden death as the first manifestation of ischaemic heart disease and to standardise the length of follow-up as well as to examine age specific subgroups, two approaches were used. The life table method disclosed that for men 35 to 44 years of age at development of complete left bundle-branch block the five-year probability of survival without sudden death was 1·0, for men 45 to 54 years of age it was 0·85, and for men 55 to 64 years of age it was 0·75. Only two sudden deaths occurred after five years of observation and both were over 10 years later. Two individuals died from malignancies (12 and 28 years) and one from stroke (one year) after the development of left bundle-branch block. The five-year incidence of sudden death as the first manifestation of heart disease was calculated for men with left bundle-branch block onset between 45 and 54 years and 55 and 64 years of age at development of left bundle-branch block and compared with men in five-year age groups without left bundle-branch block. Though the incidence rates are based upon a small number of cases of left bundle-branch block, they are at least 10 times greater than the five-year incidence of sudden death as the first manifestation of ischaemic heart disease in the remainder of the series free of left bundle-branch block (Table 2).

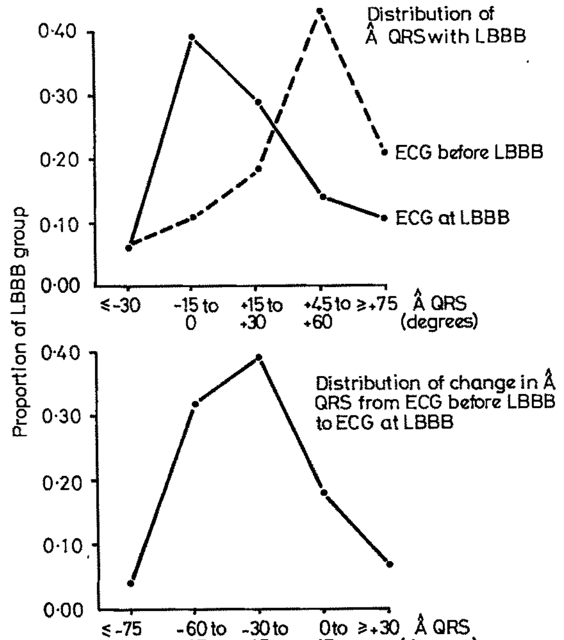

Fig. 1 *The distribution of mean frontal plane QRS axis (Å QRS) on the electrocardiogram immediately before and at development of left bundle-branch block* (top panel). *In addition the distribution of the change in the QRS axis with the development of the conduction defect is shown in the bottom panel.*

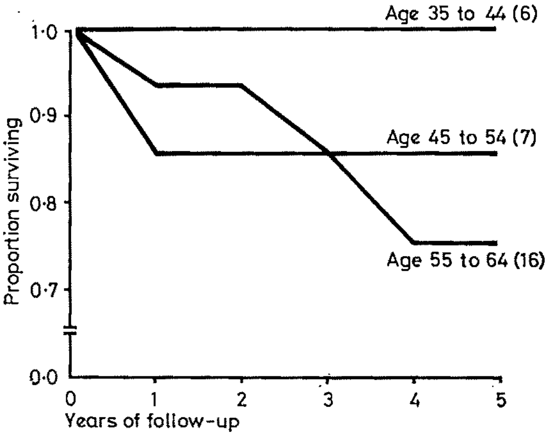

Fig. 2 *The proportion surviving after detection of left bundle-branch block according to the age at detection. The number of cases is shown in parentheses. Only one man in the 55 to 64 year age group was lost to follow-up: he died from a stroke after one year.*

Examining the mean frontal plane axis of QRS and QRS duration to determine whether these variables would identify subsets of left bundle-branch block with a poor prognosis, the ages 45 to 64 were combined because there was no significant correlation between age and either of these two electrocardiographic variables in the presence of left bundle-branch block. For QRS duration there was no difference in early mortality but there was a trend towards increased long-term mortality for wide QRS duration (Fig. 3); also two subjects with left bundle-branch block and QRS widening died after the first five years. The mean frontal plane axis of QRS did not differentiate those with an adverse or favourable prognosis (Fig. 3). Only two of those with a QRS axis of less than 0°, however, had pronounced left axis deviation, both of them had it before the development of left bundle-branch block. One is still alive after nine years of follow-up and the other died of a stroke after one year of follow-up.

Table 2 *Five-year incidence of sudden death as only manifestation of heart disease*

Complete left bundle-branch block (LBBB)	
Age at LBBB	*Five-year incidence sudden death/1000*
45 to 54	143
55 to 64	183
No LBBB	
Age free of ischaemic heart disease and LBBB	*Five-year incidence sudden death/1000*
45	0·8
50	3·1
55	4·7
60	8·1
65	18·9

Discussion

PROGNOSIS

Discussion of the prognosis for left bundle-branch block in this series should be preceded by the examination of several factors including the population from which the data were derived. Though there is concern that none of the groups for study of cardiovascular disease is representative of general population,[15] the Manitoba study is a highly selected series, and extrapolation of our findings to the general population must be done with caution. However, the relatively young age at entry and the repeated examinations permit identification of age at development and factors associated with the development of left bundle-branch block. The small number of cases of left bundle-branch block suggests caution in the extrapolation of the data. Clinically, *occult* ischaemic heart disease may have been responsible for the development of left bundle-branch block in some cases and thus have influenced the prognosis.

The prognosis reported for complete left bundle-branch block has varied widely, mainly as a result of the different populations from which the cases were selected, presence or absence of heart disease, and the type and severity of heart disease. Initial studies from hospital-based populations of ill patients disclosed a high prevalence of disease, with an average survival of 1·5 to 4·0 years.[16–19] Later studies of armed forces personnel and outpatients with left bundle-branch block with no evidence of heart disease disclosed no adverse prognosis.[20–22] Population studies have reported conflicting findings. Two studies reported an increased mortality[23 24] while another two[1 25] found little or no increased risk of death from ischaemic heart disease. In our study left bundle-branch block, developing in men over 45 years of age, is associated with an increased mortality usually within the first five years of development. One possible explanation for the apparently conflicting observations is that mortality rate is influenced by the proportion of left bundle-branch block of recent onset.

Electrocardiographic features such as QRS duration and frontal plane QRS axis did not identify subgroups with a significantly different outcome though a wide QRS duration *may* point to an unfavourable long-term prognosis. Johnson *et al.*,[18] studying left bundle-branch block in patients with relatively severe heart disease, observed that survival was inversely proportional to QRS duration which they believed reflected the severity of the heart disease. For persons without apparent heart disease the electrocardiographic measurement of QRS duration was not a powerful prognostic factor. Electrophysiological intracardiac measurements of intraventricular conduction times are undoubtedly a more sensitive indicator of the severity of conduction system disease and prognosis.[26 27]

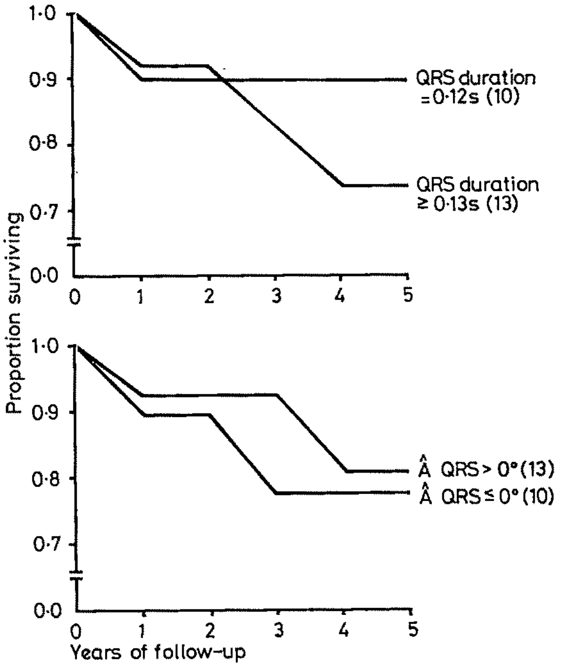

Fig. 3 *The proportion surviving after detection of left bundle-branch block according to QRS duration* (upper panel) *and mean frontal plane QRS vector (Â QRS).*

In this study, cardiac mortality consisted of sudden death mainly in persons who developed no clinical evidence of ischaemic heart disease in the interval between development of left bundle-branch block and death. Left bundle-branch block after myocardial infarction or in patients with angina pectoris has been identified as a predictor of sudden death,[19 28 29] but a similar relation has not been observed in the absence of ischaemic heart disease.

It is important to recognise and define high-risk groups and the nature of the relation between left bundle-branch block and sudden death remains to be determined. Speculations on this relation include the possibility that persons with left bundle-branch block are more likely to develop complete heart block or fatal arrhythmias should ischaemic heart disease subsequently occur. In addition, though cardiovascular epidemiological studies label sudden death as one form of ischaemic heart disease, sudden death in left bundle-branch block may result from heart block or arrhythmias unrelated to ischaemic heart disease.

ANTECEDENT ELECTROCARDIOGRAPHIC FINDINGS

The electrocardiogram was of limited value in predicting the development of left bundle-branch block. The majority of previous electrocardiograms in this group had been normal. Left ventricular hypertrophy, though relatively infrequent, was the only electrocardiographic abnormality that was an important antecedent of left bundle-branch block. This is consistent with the data of Bauer[30] whose much smaller group, however, consisted of patients with clinical evidence of heart disease. Of interest is the low proportion of cases with previous electrocardiographic findings of incomplete left bundle-branch block or pronounced left axis deviation referred to as left anterior hemiblock.[31] The 7 per cent prevalence of previous distinct left axis deviation in this study is similar to that in preliminary reports from Framingham.[23] The small proportion with earlier distinct left axis deviation suggests that the site of the block may not involve the anterior part of the left bundle and is proximal—predivisional, as suggested by Rosenbaum.[31] An equally acceptable explanation, however, is that left bundle-branch block occurs without warning signs.

CHANGES ASSOCIATED WITH OCCURRENCE OF LEFT BUNDLE-BRANCH BLOCK

In the early days of electrocardiography it was believed that the development of left bundle-branch block was associated with changes in mean frontal QRS vector.[2] Later investigators disputed these findings and reported that development of left bundle-branch block was infrequently associated with obvious shifts in QRS axis.[3 4] The present investigation has shown a statistically significant mean leftward shift in the QRS axis of 22 degrees with the development of left bundle-branch block. This was considerably greater than the expected change in the QRS axis over a similar time interval in men who did not develop this intraventricular conduction defect.

The development of left bundle-branch block thus usually occurs without preceding electrocardiographic abnormalities. Previous left ventricular hypertrophy, though infrequent, is the only significant antecedent finding. In the absence of clinical evidence of ischaemic or valvar heart disease the prognosis of left bundle-branch block is more favourable than in patients with heart disease with this conduction disturbance. However, a significant increased proportion of sudden deaths was observed in this group mainly in the first few years after the onset of left bundle-branch block.

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Left ventricular hypertrophy in presence of complete left bundle-branch block*

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SUMMARY Electrocardiograms of 2500 consecutive patients who died in hospital were reviewed in order to study the relation of complete left bundle-branch block to pathological determinants of anatomical left ventricular hypertrophy. Of these, 43 patients demonstrated complete left bundle-branch block and all but two had anatomical left ventricular hypertrophy at necropsy. Mean values of total heart weight and percentage total heart weight of normal were significantly higher in this group of 43 patients with complete left bundle-branch block than in a control necropsy group of 300 patients with anatomical left ventricular hypertrophy but without complete left bundle-branch block. Left ventricular wall thickness did not correlate with other measures of left ventricular muscle mass. Commonly used electrocardiographic voltage criteria for left ventricular hypertrophy identified approximately one-half of the 41 patients with left bundle-branch block and anatomical left ventricular hypertrophy. The degree of electrocardiographic voltage abnormality correlated modestly with total heart weight and percentage total heart weight of normal. A group of 25 patients was studied in whom electrocardiograms were available before and after complete left bundle-branch block. Normal voltage before left bundle-branch block tended to remain normal, while abnormally high voltage tended to fall after complete left bundle-branch block developed. Complete left bundle-branch block in a necropsy population characterised a group with extreme anatomical left ventricular hypertrophy. The sensitivity of the usual electrocardiographic left ventricular hypertrophy voltage criteria in the presence of complete left bundle-branch block is only slightly less than in patients with left ventricular hypertrophy alone. The degree of electrocardiographic voltage abnormality with complete left bundle-branch block shows modest correlation with degree of anatomical left ventricular hypertrophy.

Opinions vary as to whether or not the electrocardiographic diagnosis of left ventricular hypertrophy can be made when complete left bundle-branch block coexists.[1–3] Few data have been reported on the subject, and reports suffer somewhat from lack of clear definition of methods and terminology. The issue may be of more than academic interest when one considers that left ventricular hypertrophy may be missed by routine chest *x*-ray film[4] and physical examination.[5] Though other clinical modalities, that is angiography and echocardiography are also available for assessment of left ventricular mass, the cornerstones for the diagnosis of left ventricular hypertrophy remain the chest *x*-ray film, physical examination, and electrocardiogram in most routine clinical settings.

The purpose of this report is to explore further how well currently employed electrocardiographic criteria for the diagnosis of left ventricular hypertrophy can be applied to a group of patients at necropsy who had complete left bundle-branch block. We also examine the electrocardiograms of a group of patients before and after the development of complete left bundle-branch block assessing its effect on the QRS voltage.

Methods

Electrocardiograms of 2500 consecutive patients who died at Strong Memorial Hospital in Rochester, New York, during the years 1972 to 1976 were

*This study was supported in part by a grant from the National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, Maryland; Genesee Valley Heart Association Research Fellowship Grant, Rochester, New York; and grant-in-aid from the Genesee Valley Heart Association. Presented in part at the 50th Scientific Sessions, American Heart Association, Miami Beach, Florida, 30 November 1977.

Received for publication 14 July 1979

reviewed. Records were selected for study if the patient was 21 years or older and if complete left bundle-branch block was recorded within six months of death. Patients who developed complete left bundle-branch block as a terminal event (within 24 hours of death) were excluded. All the following criteria were required for the diagnosis of complete left bundle-branch block: (1) documented atrioventricular conduction, (2) absence of Wolff-Parkinson-White syndrome, (3) QRS duration in any lead ≥120 ms, (4) intrinsicoid deflection ≥50 ms in the left heart leads, (5) deformity of the R wave in the left heart leads consisting of slurred, notched, flat, or bifid R wave, (6) major fraction of the QRS duration in the left heart leads occupied by the R wave, (7) absence of significant Q waves in any left heart lead,[6] (8) absence of a large S wave (≥20% of the total QRS deflection) in any left heart lead, and (9) ST segment depression and/or T wave inversion in the left heart leads.

The 43 patients that met the above criteria were subdivided into (a) a group of 32 patients with persistent complete left bundle-branch block (present for at least six months without intervening normal conduction) or left bundle-branch block of indeterminate onset and (b) a group of 11 patients in whom the onset of complete left bundle-branch block occurred within six months of death or in whom it was intermittent. The former group of 32 patients is termed persistent complete left bundle-branch block for the sake of conciseness, while the latter group of 11 patients is termed intermittent left bundle-branch block, though, strictly speaking, some of these simply represent recent onset left bundle-branch block.

As a control group, the electrocardiograms and findings at necropsy of all patients age 21 years or more who came to necropsy during the first three months of each year during the study period 1972–76 were reviewed.

The total heart weight, left ventricular wall thickness, body length, and sex were recorded at necropsy. Normal predicted total heart weight was defined according to the tables of Zeek,[7] and any heart weight two standard deviations above the mean of normal was regarded as anatomical left ventricular hypertrophy. Percentage total heart weight of normal was calculated for each patient at necropsy by dividing the recorded total heart weight by the predicted value. This measurement allows correction of total heart weight for sex and body length.

One investigator coded by number all electrocardiograms without knowledge of the results of the necropsies. The following electrocardiographic measurements (paper speed 25 mm/s, sensitivity 1 mV/10 mm) were then recorded by blinded observers: (1) height (mV of R waves in leads I, II, II, aVL, aVF, and V1 to V6; (2) depth (mV) of S waves in leads I, II, III, aVL, aVF, V1 to V6; (3) intrinsicoid deflection (ms) from the left heart leads; (4) maximum QRS width (ms) from any lead; and (5) mean QRS axis. Electrocardiographic voltage criteria for left ventricular hypertrophy were reviewed, and those criteria shown by Romhilt and co-workers[8] to have a higher predictive value for left ventricular hypertrophy were tested. Electrocardiogram and necropsy data were transferred to IBM punch cards for computerised statistical analysis.

Electrocardiographic variables were compared with pathological determinants of left ventricular hypertrophy using standard correlational analyses. Student t tests (two-sided) were used to compare pathological determinants of left ventricular hypertrophy in the various subgroups of patients at necropsy. McNemar's test (exact version) was employed to determine statistically significant change in electrocardiographic variables before and after development of complete left bundle-branch

Table 1 *Identification of patient groups*

Patient groups			*Number of patients*			*Mean age (y)*
			Total	*Male*	*Female*	
Total patient records reviewed			2500	—	—	—
Patients with complete LBBB			90	—	—	—
Necropsy patients with complete LBBB	Patients with persistent* LBBB		32	24	8	66·4
	Patients with intermittent* LBBB		11	8	3	63·5
Patients with intermittent* LBBB	Necropsy		11	8	3	63·5
	No necropsy		14	7	7	62·9
Control† necropsy population	Anatomical LVH‡	LBBB	11	7	4	63·3
		No LBBB	300	160	140	66·1
	No anatomical LVH‡	LBBB	1	1	0	65·0
		No LBBB	168	101	67	58·3

* See text for definition of persistent and intermittent LBBB. † Control (base) necropsy population defined in text. ‡ Anatomical LVH is described in text. LBBB, left bundle-branch block; LVH, left ventricular hypertrophy.

block in a group of 25 patients in whom both types of electrocardiograms were available within six months of each other.

Results

The sex and mean age of the patient groups are shown in Table 1. Forty-three of 90 patients (47·7%) who died with complete left bundle-branch block came to necropsy. The average percentage of necropsy examinations for the entire hospital population during this period of study was 53·2.

Table 2 *Clinicopathological findings in 43 patients with complete left bundle-branch block and necropsy*

Diagnosis	*Number*	*Per cent*
Old or recent myocardial infarction*	31	72·1
Aortic valve disease†	4	9·3
Cardiomyopathy	4	9·3
Normal heart	2	4·6
Pulmonary embolism	1	2·3
Cor pulmonale	1	2·3
Total	43	100·0

* Significant hypertension was additionally present in five of tnese patients † An additional five patients had significant aortic valve disease in association with old or recent myocardial infarction and are included in the latter category.

Of the patients with complete left bundle-branch block, 41 of 43 (95·3%) had evidence of anatomical left ventricular hypertrophy on the basis of total heart weight and percentage total heart weight of normal. Left ventricular wall thickness showed no correlation with total heart weight ($r = -0·05$) and percentage total heart weight of normal ($r = -0·05$).

The control necropsy group consisted of 480 patients, 311 (64·8%) of whom were found to have anatomical left ventricular hypertrophy; 12 of 480 (2·5%) also showed complete left bundle-branch block within six months of death. Only one of the 169 control patients without left ventricular hypertrophy had left bundle-branch block, while 11 of the 311 control patients with left ventricular hypertrophy had left bundle-branch block.

Table 2 summarises the clinical information of 43 patients with complete left bundle-branch block at necropsy.

Table 3 summarises the comparison of mean relative heart weights in the groups of patients mentioned. The entire group of 43 patients with left bundle-branch block and the subgroup of 32 patients with persistent left bundle-branch block both demonstrate a significantly higher mean relative heart weight than do the subgroup of 11 patients with intermittent left bundle-branch block and the group of 300 control patients with anatomical left ventricular hypertrophy but no left bundle-branch block ($P < 0·05$).

Table 3 *Comparison of percentage total heart weight of normal in groups of patients with and without complete left bundle-branch block*

Group	*Number of patients*	*Percentage total heart weight of normal ±SD*
Complete LBBB	43	200·4 ±49·9*
Persistent* LBBB	32	209·7 ±54·3*
Intermittent† LBBB	11	175·6 ±37·8
LVH but no LBBB (control)	300	169·1 ±36·2

*Significantly higher than in the last two groups ($P < 0·05$).
†See text for definition of persistent and intermittent LBBB.
LBBB, left bundle-branch block; LVH, left ventricular hypertrophy; SD, standard deviation.

Table 4 shows the results of application of currently employed electrocardiographic voltage criteria for left ventricular hypertrophy to the group of 41 patients with complete left bundle-branch block and anatomical left ventricular hypertrophy. A comparison of the expected frequency of abnormality (on the basis of Romhilt *et al.'s*[8] data for patients with left ventricular hypertrophy but no left bundle-branch block with observed frequency of abnormality is shown. The data reveal only a minor loss of sensitivity of these criteria in our group of patients with complete left bundle-branch block.

Table 4 *Frequency of abnormality of left ventricular hypertrophy voltage criteria in 41 patients with complete left bundle-branch block and anatomical left ventricular hypertrophy*

*Voltage criteria**	*Normal* value (mm)*	*Observed frequency of abnormality* (%)	*Expected frequency* of abnormality* (%)
RaVL	⩽ 7·5	46·3	22·5
(RI+SIII) – (RIII+SI)	< 17·0	26·8	17·5
SV1 or SV2+RV5	< 35·0	51·2	56·3
SV1 or SV2+RV5 or RV6	⩽35·0	53·7	55·6
R+S†	⩽40·0	48·8	55·0
RS‡	⩽35·0	36·6	40·6
SV1 or SV2	< 30·0	34·1	—
SV1 or SV2 or SV3	⩽30·0	34·1	—
RV5 or RV6	< 30·0	4·9	—
SV1 or SV2 or SV3 or RV5 or RV6	< 40·0	48·8	—

* From data by Romhilt *et al.*[8] in patients with anatomical left ventricular hypertrophy but no left bundle-branch block.
† Sum of largest R wave and largest S wave in unipolar praecordial leads. ‡ Largest total RS deflection in any unipolar lead.

Table 5 shows the correlation of three voltage criteria (two of which were the most sensitive as found in this study) with the total heart weight, percentage total heart weight of normal, and left ventricular wall thickness of the 41 patients with

Table 5 *Correlation of electrocardiographic variables with measures of anatomical left ventricular hypertrophy in 41 patients with complete left bundle-branch block and anatomical left ventricular hypertrophy*

Electrocardiogram variable	*Correlation with*		
	Absolute heart weight	*Relative heart weight (percentage of normal)*	*Left ventricular wall thickness*
RavL	0·375*	0·370*	0·212
SV1 or SV2+RV6	0·346*	0·359*	0·218
SV1 or SV2+RV5 or RV6	0·373*	0·407*	0·184
Max. QRS width	0·014	0·008	−0·211
Intrinsicoid deflection	0·155	0·216	0·090

* Significant at 5 per cent level.

complete left bundle-branch block and anatomical left ventricular hypertrophy. Left ventricular wall thickness showed no significant correlation with any of the electrocardiographic variables listed. All three voltage criteria correlated modestly with the measures of absolute and relative heart weight. There was no significant correlation of maximum QRS width or intrinsicoid deflection to any of the measurements of anatomical left ventricular hypertrophy.

Fourteen of the 43 patients with complete left bundle-branch block and necropsy showed a normal QRS axis, that is a mean QRS axis between −29 and +119 degrees, on their premortem electrocardiograms, while 29 showed left axis deviation, that is a mean QRS axis equal to or greater than −30 degrees. There was no correlation of mean QRS axis with total heart weight ($r = -0·07$) or percentage total heart weight of normal ($r = -0·05$) in the entire group of 43 patients.

Analysis of the 25 patients with electrocardiograms recorded before and after the development of complete left bundle-branch block within six months of each other disclosed that the most sensitive voltage criteria found in our study (SV1 or SV2+RV5, SV1 or SV2+RV5 or RV6, and R+S) when abnormal before left bundle-branch block tended to become normal after the development of left bundle-branch block ($P < 0·05$). When these three voltage criteria were normal before left bundle-branch block, they tended to remain normal after left bundle-branch block developed (Fig.). No clear pattern of change was noted in the other electrocardiographic criteria tested.

Discussion

The high incidence of anatomical left ventricular hypertrophy in 43 patients with complete left bundle-branch block (95·3%) is not surprising since almost all our patients with left bundle-branch block had other associated cardiovascular disease. The strong association of anatomical left ventricular hypertrophy and other cardiovascular disease (especially hypertension and coronary artery disease) in patients with complete left bundle-branch block has been noted by others.[9–11] The severity of anatomical left ventricular hypertrophy in our population of 43 patients was unexpected. Mean heart weights and relative heart weights were twice normal predicted values. Furthermore, the mean heart weight of the 43 patients with complete left bundle-branch block was significantly higher ($P < 0·05$) than the mean heart weight of the 300 control necropsy patients with anatomical left ventricular hypertrophy but without complete left bundle-branch block. Interestingly, the mean heart weight in the subgroup of 11 patients with intermittent and recent onset left bundle-branch block was significantly lower ($P < 0·05$) than in the subgroup of 32 patients with persistent and indeterminate onset left bundle-branch block. This suggests, though does not prove, a progression of anatomical left ventricular hypertrophy in association with the development of complete left bundle-branch block.

Although sensitivity of currently employed electrocardiographic voltage criteria for left ventricular hypertrophy is relatively low when applied to our population of 41 patients with complete left

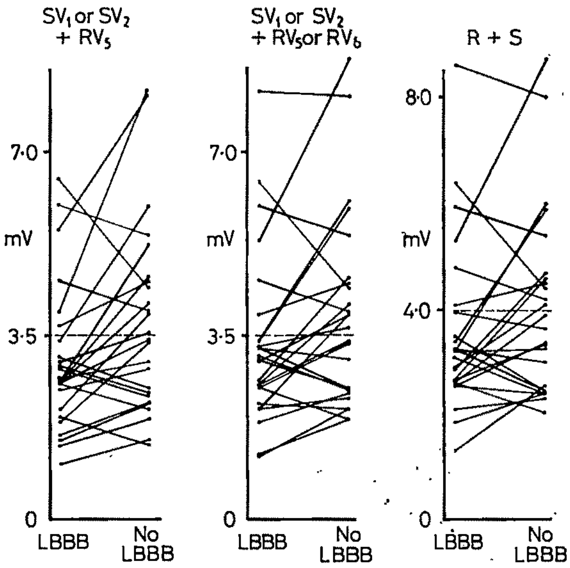

Fig. *Change in electrocardiographic voltage in 25 patients before and after development of complete left bundle-branch block.*

bundle-branch block and anatomical left ventricular hypertrophy (26·8~53·7%), the sensitivity is only slightly less than when the same criteria are applied to a group of patients with anatomical left ventricular hypertrophy but without left bundle-branch block (17·5~56·3%) according to Romhilt *et al.*'s[8] data. Pathological criteria for anatomical left ventricular hypertrophy in our study differ from those used by Romhilt *et al.*[8] who used weight of the isolated left ventricle as the criterion for anatomical left ventricular hypertrophy while we used total heart weight and total heart weight corrected for sex and body length as suggested by Zeek.[7] Perhaps the sensitivity of the electrocardiographic voltage criteria we tested would have differed had we employed the same pathological method as Romhilt's group. Weight of the separated left ventricle appears to be a superior pathological measure of anatomical left ventricular hypertrophy than total heart weight even if the total heart weight is corrected for sex and body length, though most necropsy laboratories (including ours) do not employ this technique.[12 13] Pathologically, left ventricular wall thickness has not been shown to correlate well with any other indices of left ventricular muscle mass,[12–14] and the absence of correlation of this measurement in our study with electrocardiographic and other pathological criteria of left ventricular hypertrophy supports this observation. Our data regarding the sensitivity of various electrocardiographic voltage criteria for left ventricular hypertrophy in the presence of complete left bundle-branch block tend to parallel the recent findings of Cokkinos *et al.*[3] who showed good correlation of pre- and post-left bundle-branch block Sokolow index values in a group of 40 patients with intermittent complete left bundle-branch block.

Interestingly, if one employs our most sensitive electrocardiographic voltage criteria as shown in the Fig. to the group of 25 patients with pre- and post-left bundle-branch block electrocardiograms, patients without electrocardiographic voltage criteria for left ventricular hypertrophy before the development of complete left bundle-branch block tend to retain normal voltage after complete left bundle-branch block develops while those with abnormally high voltage before left bundle-branch block tend to lose it after complete left bundle-branch block develops. This observation, plus the fact that our most sensitive electrocardiographic voltage criteria correlate modestly with total heart weight and percentage total heart weight of normal in 41 patients with both anatomical left ventricular hypertrophy and complete left bundle-branch block, suggest that when abnormal electrocardiographic voltage remains in a patient with complete left bundle-branch block, anatomical left ventricular hypertrophy must certainly be suspected. The mere presence of complete left bundle-branch block in our population is associated with extreme left ventricular hypertrophy in nearly all (95·3%) patients. Perhaps, though not very sensitive, the presence of complete left bundle-branch block may be a specific marker of underlying anatomical left ventricular hypertrophy as judged by our study and that of Scott's.[15] Exact specificity of the electrocardiographic variables for left ventricular hypertrophy in the presence of complete left bundle-branch block cannot be accurately gauged by this study since only two of 43 patients with complete left bundle-branch block were found not to have anatomical left bundle-branch block.

We were unable to show a difference in total heart weight and percentage total heart weight of normal between patients with complete left bundle-branch block and normal QRS axis and patients with complete left bundle-branch block and left axis deviation. However, recent data[10] suggest that patients with both complete left bundle-branch block and left axis deviation experience more severe cardiac diseases, with more deaths from cardiovascular events than do patients with complete left bundle-branch block but with normal QRS axis.

The population sampled by our study differs considerably from the population of all persons with left bundle-branch block, and caution must be exercised in extending these findings to that population. A group of generally younger patients has been described[16 17] who have complete left bundle-branch block but no other evidence of heart disease. The magnitude and status of this group are of principal interest. Since such patients were rarely encountered (1/12 of those with complete left bundle-branch block) in our control necropsy population of 480 patients, it appears that they either comprise a very small portion of the population of persons with left bundle-branch block or that they develop anatomical left ventricular hypertrophy at a higher rate than persons without left bundle-branch block. Perhaps some of the population of young persons with asymptomatic complete left bundle-branch block do indeed have a degree of anatomical left ventricular hypertrophy not detectable clinically, or longer follow-up of these persons would eventually reveal that anatomical left ventricular hypertrophy develops as a result of previously undetected associated heart disease.

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Br Heart J 1980; **43:** 176–183

Five-year survival of 728 patients after myocardial infarction

A community study

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SUMMARY This study deals with the five-year survival of 728 myocardial infarction patients who survived the first 28 days after the onset of symptoms. The series was collected by the Helsinki Coronary Register and includes all cases of acute myocardial infarction in the population who were under 66 years of age during the period 1 July 1970 to 30 June 1971. Of the 219 patients who subsequently died, 81·8 per cent died from ischaemic heart disease. The mortality was highest during the first year after the acute phase but did not decrease after the second year. The mortality was higher in patients with a transmural infarction (five-year mortality 34·0%) compared with those with a nontransmural infarction (19·7%). The mortality also was higher for recurrent acute myocardial infarctions than for first attacks. The five-year mortality for women was less (20·5%, age-adjusted) than for men (31·6%). This is mainly because of the higher incidence of nontransmural infarcts in women. Acute ischaemic heart disease is more common, more often fatal, and has a poorer long-term prognosis in men than in women in Helsinki. The acute mortality from acute ischaemic heart disease is high in Helsinki when compared with other WHO registers and, in addition, the long-term prognosis seems to be relatively poor in Helsinki.

The Coronary Registers co-operating with WHO gather community-based data of the severe forms of acute ischaemic heart disease, both acute myocardial infarctions and sudden coronary deaths. The Helsinki Coronary Register started on 1 September 1969, and a series of 1224 patients who suffered an attack of acute ischaemic heart disease within one year from 1970 to 1971 has now been followed for five years. Previous long-term follow-up studies have usually been based on hospital series. In countries in which only some of the patients with acute myocardial infarction are treated in the hospital, hospital series tend to include a large number of more severe cases, and their follow-up may give a less favourable overall prognosis for this disease. In Finland, nearly all patients with acute myocardial infarction are treated in hospitals, but concentration of severe cases might take place in hospitals provided with a coronary care unit. A non-selected series collected by a coronary register provides a good opportunity for the study of long-term prognosis after acute myocardial infarction.

Received for publication 14 May 1979

The high acute myocardial infarction attack rate among Finns and their high early mortality have been shown in several studies,[1–5] but it is not known if the long-term prognosis after myocardial infarction is worse than elsewhere.

In the present study the five-year survival after the acute phase of acute myocardial infarction of the 728 patients from the Helsinki Coronary Register was studied in relation to age, sex, previous infarction, and transmural infarction.

Patients and methods

The Coronary Register in Helsinki records all cases suspected of having an attack of acute ischaemic heart disease among residents of Helsinki under 66 years of age. The completeness of recording is checked in many ways. A detailed description of the operation of the WHO Registers and in particular of the Helsinki Register[5] has been published previously.[6–8] Collection of data was almost complete for deceased cases as the death certificates of all Helsinki residents are sent to the municipality of residence regardless of the place of the attack. There is some loss among those suffering an attack outside Helsinki, since if they survive and are previously on a disability pension they may be left outside the Register. The number of such patients is, however, very small.

All of the patients entered in the Register were interviewed by the Register's nurse as soon as the patient's clinical state allowed. In 28 days the patients were classified on the basis of pain anamnesis, enzyme, and electrocardiographic findings into the diagnostic categories according to the directives issued by WHO.[5] The criteria for the categories were as follows:

Definite acute myocardial infarction: The patients with unequivocal serial electrocardiographic changes; or typical history of chest pain and raised serum enzyme levels or equivocal electrocardiographic changes and raised enzymes.

Possible acute myocardial infarction: The patients with typical chest pain, but insufficient evidence to include the case under definite acute myocardial infarction and no good evidence for another diagnosis.

An additional classification of acute myocardial infarction as transmural or nontransmural was possible in 87 per cent of patients surviving the acute phase on the basis of the electrocardiographic findings as follows:

Transmural acute myocardial infarction: The development of a typical rise in the ST segment (> 1 mm), inversion of the T wave, and pathological Q wave in a serial electrocardiogram, or a diagnostic combination of these in the only electrocardiogram taken in a case classified as acute ischaemic heart disease according to the criteria given above.

Nontransmural acute myocardial infarction: ST segment depression and/or symmetrical T wave inversions developing and persisting in serial electrocardiograms without QRS changes, or corresponding changes found in the only electrocardiogram taken in a case classified as acute ischaemic heart disease according to the criteria given above. Cases in which the changes may have been caused by digitalis, electrolyte disturbances, or other such factors were omitted.

The series used in this study comprised patients under 66 years of age suffering an acute myocardial infarction during the period 1 July 1970 to 30 June 1971, and surviving the first 28 days. Originally, 1224 patients suffered an attack of acute ischaemic heart disease during the one-year period, and 728 patients (59·5%) survived the first 28 days. Each patient was included in the series only once.

The patients received a questionnaire from the Register every year during the five years' follow-up time. It was always sent at the same time of the year as the patient had suffered his infarction, with the latitude of a week. The 428 patients who answered the fifth year's questionnaire were classified as survivors. The survival of the other 300 patients was checked at first from the Helsinki Coronary Register. The data on deaths were obtained from the Register if the patient had died from acute ischaemic heart disease at less than 65 years of age. The survival of the rest of the patients was checked by the personnel of the Register from the microfilms which are published annually by the Finnish officials, and include the name, the social security number, and the data on all deaths in Finland. The official statistics of deaths in Finland is very accurate and reliable, and it is practically impossible for any death to escape the official statistics. After checking the survival of every patient in the series, the cause of death for the deceased patients was obtained from the Death Cause Register of the Statistical Office of the City of Helsinki, which collects the death certificates of the Helsinki inhabitants regardless of the place of death. The cause of death was classified as ischaemic heart disease if the basic or immediate cause of death given in the certificate was a fresh myocardial infarction or chronic ischaemic heart disease or a state after previous acute myocardial infarction without other cause of death. Thus, by using information from the questionnaires, the files of the Helsinki Coronary Register, and the official statistics, it was possible to find out the survival time for all patients with the exactness of one day during the follow-up time. In addition, it was possible to know the cause of death for all deceased patients.

The age adjustment used in the study was made using the direct method.[8] The statistical tests were carried out using the Mantel-Haenszel test[9] for the data stratified as regards age, and the usual χ^2 test in other cases. The use of the latter is indicated in the text within parentheses.

Results

Of 1224 patients from Helsinki who suffered an attack of acute ischaemic heart disease during the period 1 July 1970 to 30 June 1971, 728 patients were alive after the first 28 days. Of these 728 patients, 77·3 per cent were classified as definite acute myocardial infarction and 22·7 per cent as possible acute myocardial infarction; 30·1 per cent of the patients were women. In 77·7 per cent of all patients the infarction was the first. The distri-

Table 1 *Cumulative five-year mortality of men with a primary or recurrent acute myocardial infarction who survived 28 days, expressed as percentage*

	6 months		*1 year*		*2 years*		*3 years*		*4 years*		*5 years*		*N*	
Age (y)	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*
≤44	0	12·5	3·5	25·0	10·3	37·5	15·5	37·5	17·2	37·5	17·2	37·5	58	8
45–49	7·6	13·3	7·6	13·3	11·3	13·3	11·3	20·0	15·1	33·3	17·0	33·3	53	15
50–54	7·7	4·4	11·5	13·0	16·7	26·1	19·2	34·8	24·4	43·5	25·6	56·5	78	23
55–59	6·9	10·0	10·9	10·0	13·9	23·3	20·8	30·0	22·8	56·7	38·4	60·0	101	30
60–64	6·7	12·5	16·9	15·0	23·6	22·5	28·1	30·0	31·5	32·5	36·0	42·5	89	40
65	11·1	40·0	11·1	40·0	33·3	60·0	33·3	60·0	33·3	60·0	66·7	60·0	9	5
Total	6·2	11·6	10·8	14·9	16·2	24·8	20·4	31·4	23·5	42·1	26·3	46·3	388	121
Standard		11·0		15·2		25·3		31·4		42·5		48·3		

Table 2 *Cumulative five-year mortality of women with a primary or recurrent acute myocardial infarction who survived 28 days, expressed as percentage*

	6 months		*1 year*		*2 years*		*3 years*		*4 years*		*5 years*		*N*	
Age (y)	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*	*First*	*Previous*
≤44	0	0	0	0	0	0	0	0	0	0	0	0	5	1
45–49	0	0	0	0	8·7	0	13·7	0	13·0	0	17·4	0	23	2
50–54	0	0	3·6	0	3·6	0	3·6	0	3·6	0	7·1	25·0	28	4
55–59	4·9	0	9·8	0	14·6	0	14·6	0	22·0	10·0	22·0	20·0	41	10
60–64	6·8	20·0	11·0	30·0	17·8	35·0	21·9	40·0	27·5	55·0	31·5	65·0	72	20
65	0	0	0	25·0	0	25·0	0	25·0	22·2	25·0	22·2	50·0	9	4
Total	3·9	9·8	7·3	17·1	12·3	19·5	14·5	22·0	19·6	31·7	22·3	43·9	178	41
Standard												37·5		

bution of the population for age, sex, and previous infarction can be seen in Tables 1 and 2.

During the five years after the acute phase 219 patients died, that is 30·1 per cent of the 728 patients. A necropsy was performed in 32·7 per cent. The cause of death of 177 patients was either a new acute myocardial infarction or chronic ischaemic heart disease with no other cause of death. Thus 80·8 per cent of deaths were the result of ischaemic heart disease. Cardiovascular diseases as a whole were the cause of a total of 91·4 per cent of the deaths (Table 3).

Table 3 *Causes of death in five-year follow-up of 728 patients with acute myocardial infarction who survived 28 days*

Cause of death	*No.*	*Per cent*
Ischaemic heart disease	177	80·8
Other heart disease than ischaemic heart disease	3	1·4
Other cardiovascular disease than cardiac disease	20	9·1
Other than cardiovascular disease	19	8·6
Total	219	100·0

Mortality after the acute phase was highest during the first year and especially during the first six months of that year. Of those who survived the acute phase, 11·0 per cent died during the 11 months following it. During the second, third, fourth, and fifth year 6·6, 4·8, 6·6, and 5·4 per cent of those alive at the beginning of each year died, respectively. For the patients who suffered their first infarction, the corresponding figures were 9·7, 5·9, 4·2, 4·6, and 3·6 per cent.

There was a difference in mortality between men and women; 26·5 per cent of the women and 31·6 per cent of the men died ($p < 0·05$) (Tables 1 and 2). The age-adjusted mortality for women was 20·3 per cent (Fig. 1). The mortality for both sexes exceeded conspicuously the mortality for the Helsinki population of the same age.

Mortality clearly increased with age: 20·1 per cent of the men and 12·9 per cent of the women (18·8% of the total) under 50 years of age died within the five years of the acute phase, whereas 35·7 per cent of the men and 28·7 per cent of the women between 50 and 65 years of age died, that is 33·4 per cent of the total.

The five-year mortality in the category 'definite acute myocardial infarction' was 32·2 per cent while it was 19·4 per cent in the category 'possible acute myocardial infarction' ($P < 0{\cdot}001$). The age-adjusted mortality in the category 'possible acute myocardial infarction' was 20·1 per cent, or slightly closer to the mortality of definite acute myocardial infarctions than to that of the Helsinki population of the same age (Fig. 2).

Of the 566 patients suffering their first acute myocardial infarction, 25·1 per cent died within the five years, whereas 47·5 per cent of the 162 patients with a recurrent acute myocardial infarction died during this period ($P < 0{\cdot}001$) (Fig. 3). Those suffering a recurrent acute myocardial infarction were older than those with a primary acute myocardial infarction, and the age-adjusted mortality for the patients with more than one infarction was 45·7 per cent.

Of the men 76·2 per cent suffered a first acute myocardial infarction, and 81·3 per cent of the women suffered a first acute myocardial infarction ($p > 0{\cdot}05$, χ^2 test). The five-year mortality among men with a primary acute myocardial infarction was 26·3 per cent and among those with a recurrent acute myocardial infarction 46·3 per cent, 48·3 per cent as adjusted for age ($p < 0{\cdot}001$) (Tables 1 and 2). There were proportionally more deaths in younger age groups in men with a recurrent acute myocardial infarction than in those with a first infarction, and, though the group with recurrent infarction consisted of older patients, the difference in five-year mortality between these groups was still present after age-adjustments. The five-year mortality among women with a primary infarction was 22·3 per cent and among those with a recurrent infarction 43·3 per cent, 37·5 per cent as adjusted for age ($p < 0{\cdot}05$) (Table 2). The five-year mortality among male patients with a primary acute myocardial infarction (26·3%) was considerably greater than that of female patients with a first infarction (17·3%, adjusted for age as regards men). The difference was not, however, statistically significant ($p > 0{\cdot}05$). The difference between the sexes in the mortality

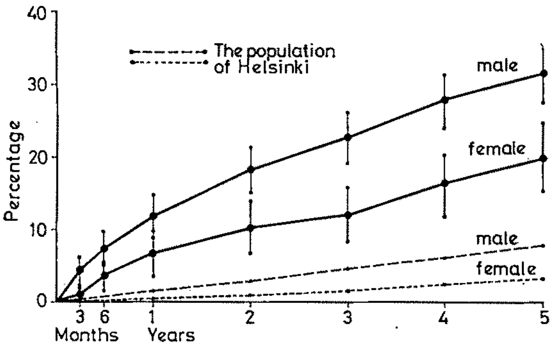

Fig. 1 *The cumulative five-year mortality with 95 per cent confidence limits among men and women after the acute phase of infarction. The figures for women are adjusted for age.*

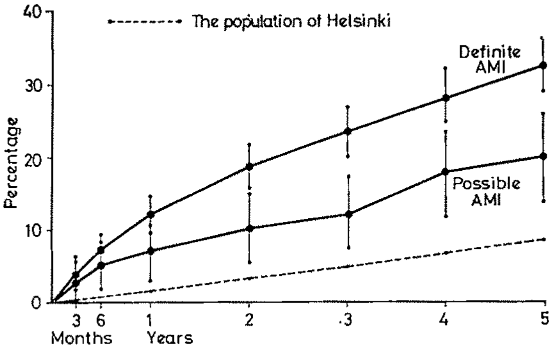

Fig. 2 *The cumulative five-year mortality with 95 per cent confidence limits in the categories 'definite acute myocardial infarction' and 'possible acute myocardial infarction' after the acute phase of infarction. The figures for the category 'possible acute myocardial infarction' are adjusted for age.*

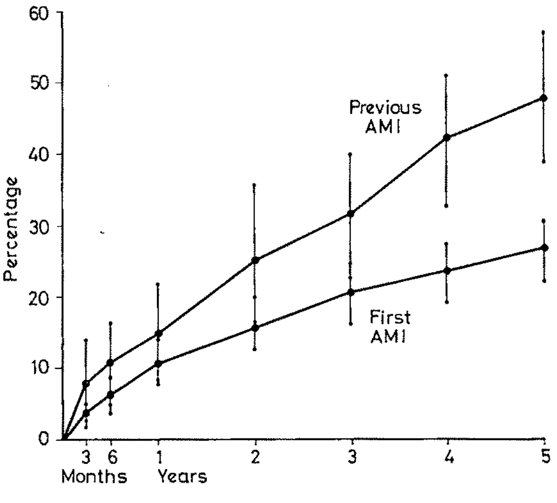

Fig. 3 *The cumulative five-year mortality with 95 per cent confidence limits of men with a primary acute myocardial infarction or a recurrent acute myocardial infarction after the acute phase of infarction. The figures for recurrent acute myocardial infarctions are adjusted for age.*

of patients with more than one infarction was also without statistical significance ($p > 0{\cdot}05$) (Fig. 4).

Of all cases, 33·8 per cent were classified as nontransmural acute myocardial infarction. In women the proportion of nontransmural acute myocardial infarction was higher; 24·2 per cent of those with transmural infarction and 42·7 per cent of those with nontransmural infarction were women ($p < 0{\cdot}001$, χ^2 test). Of the 418 patients with a transmural acute myocardial infarction 34·0 per cent died, whereas of the 213 patients with a nontransmural acute myocardial infarction 19·7 per cent died; after age adjustment the last figure was 19·5 per cent ($p < 0{\cdot}001$). There was no information on the transmurality of acute myocardial infarction in 97 patients. Mortality in this group was 35·7 per cent over a period of five years. Of the 317 men with a transmural infarction 34·7 per cent and 18·9 per cent of those 122 men with a nontransmural infarction (19·4% as adjusted for age) died during the five-year follow-up period ($p < 0{\cdot}001$) (Fig. 5). Of the 101 women with a transmural infarction 31·7 per cent, and of the 91 women with a nontransmural infarction 20·9 per cent (22·0% as adjusted for age) died within five years ($p > 0{\cdot}05$). Mortality from a nontransmural acute myocardial infarction was nearly the same among both men and women ($p > 0{\cdot}10$). Mortality among men with a transmural infarction was higher (34·7%) than that among women (23·3%, age adjusted as regards men) (Fig. 6), but this difference was not statistically significant ($p > 0{\cdot}05$).

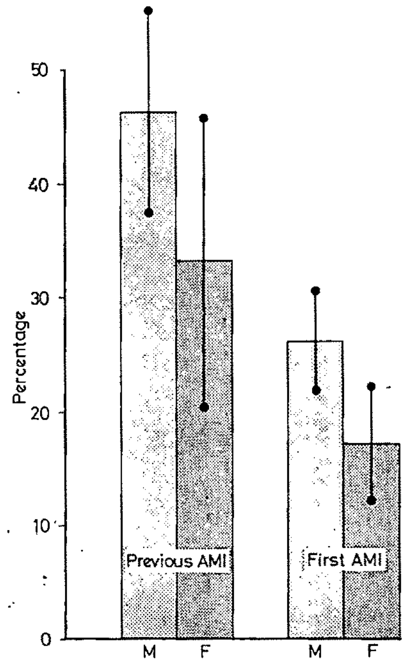

Fig. 4 *The cumulative five-year mortality with 95 per cent confidence limits of men and women for recurrent and primary infarction after the acute phase. The figures for women are adjusted for age using the age distributions of men as the standard.*

Discussion

The series used in this study comprised patients under 66 years of age who suffered a definite or probable acute myocardial infarction within a period of one year. Patients with an asymptomatic acute myocardial infarction, and the few patients who, in spite of their symptoms, did not see a physician are naturally not included in the series, but otherwise the series represents nearly all of the patients with acute myocardial infarction under 66 years of age in Helsinki during one year.

Since the WHO criteria for possible acute myocardial infarctions in survivors are, however, somewhat loose, it might be objected that there were patients in this category who in reality suffered a prolonged attack of angina pectoris. However, the number of those patients is probably small. Only 3 per cent (24) of all patients surviving the acute phase were included in the series solely on the basis of pain, and 77·5 per cent of all 728 patients surviving the acute phase fulfilled the WHO criteria of definite acute myocardial infarc-

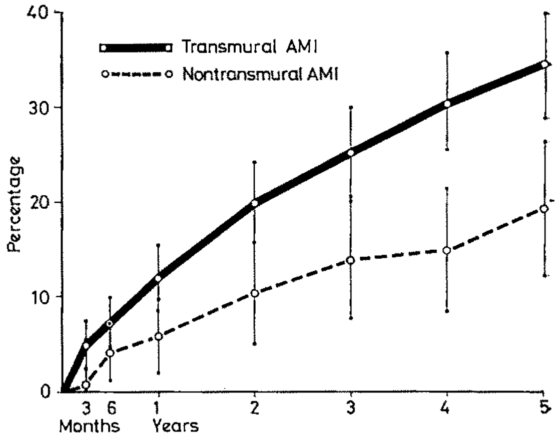

Fig. 5 *The cumulative five-year mortality with 95 per cent confidence limits among men with transmural and nontransmural infarction after the acute phase. The figures for the nontransmural acute myocardial infarctions are adjusted for age.*

tion. The five-year mortality of possible acute myocardial infarctions after the acute phase was somewhat smaller than that of definite acute infarctions. Nevertheless, when the fact that most nontransmural infarctions (which had a better prognosis) probably belonged to the category 'possible acute infarction' (c.f. the diagnostic criteria) is taken into account, the prognosis after the acute phase supports the view that a majority of the cases falling under the category 'possible acute myocardial infarction' probably consisted of patients suffering an acute myocardial infarction. The data on survival after the acute myocardial infarction were complete for each patient to the exactness of one day. The results of the study on the five-year mortality of patients with acute myocardial infarction from Helsinki can be considered reliable.

Only 32·7 per cent of those who died after the acute phase came to necropsy, but the result that about four out of five patients died of ischaemic heart disease agrees well with the results presented in studies made in other countries.[10–15] Of the patients who survived the acute phase 11·0 per cent died during the next 11 months. In the 21 WHO registers the 11-month mortality among registered cases adjusted for age and sex is 5 to 17 per cent; the figure in Helsinki is 13·9 per cent.[5] According to the results from the Coronary Register in London 7 per cent of the men and 10 per cent of the women died during the 11-month period after the acute phase.[16] Thus, the prognosis for the first year after the acute phase seems to be less favourable in the Helsinki Register, even though the differences are not very great. In the Gothenburg Register, 15·2 per cent of the patients under 65 years of age discharged from the hospital died within two years, but this evidently includes only the WHO category 'definite acute myocardial infarction'.[13] Of those counted as definite acute myocardial infarctions in the present study 19·0 per cent died within two years after the acute stage, and thus the two-year mortality is somewhat higher in Helsinki than in Gothenburg, though the differences are small.

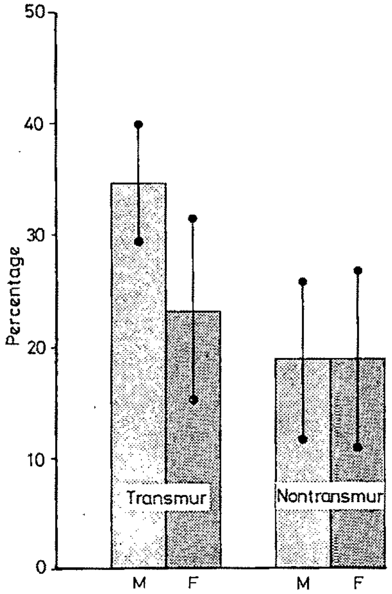

Fig. 6 *The cumulative five-year mortality with 95 per cent confidence limits of men and women with transmural and nontransmural infarction after the acute phase. The figures for women are adjusted for age using the age distributions of men as the standard.*

Long-term follow-up studies (three to five years) have been previously made on patients with acute myocardial infarction mostly using patient series in a specific hospital.[11 12 14 17–26] Patient series collected from army health care systems[27 28] and from insurance company series[29 30] have also been used in long-term follow-up studies. These series contain patients of very different types and it is difficult to compare their results since the diagnostic criteria, age and sex distribution, and severity of the cases vary in different studies. The earliest studies have been criticised for methodological errors which are considered to have made the follow-up studies in the '50s and partly even in the '60s unreliable.[31] Though the problems of selectivity of the study population are smaller in the register-based studies, the measures of frequency and outcome are sensitive, for example to the interpretation of diagnostic criteria and to the frequency and immediacy of the tests.[32] In addition, the grouping of different diagnostic categories together creates problems for comparison of studies. Evidently, not a single five-year study has yet been published using an unselected study population from a coronary register covering a large community. A four-year follow-up study from the coronary register in London has been reported, but its scope was to predict sudden death from the electrocardiogram, and it includes only patients who attended a three-month post-infarction investigation. The four-year mortality was 19·6 per cent, and the population included both definite and possible acute myocardial infarctions.[15] In the present study the corresponding four-year mortality for those under 65 years of age and alive three months after infarction was 24·0 per cent. Previous follow-up studies give a five-year mortality of 18 to 44 per cent for those who survived the acute phase, depending on the age and sex structure and severity of the disease. In comparison, in spite of the problems, the 30·1 per cent five-year mortality in unselected patients with acute myocardial infarction under 66 years of age in the present study does, however, seems quite large compared with the results of previous studies. The mortality in the category 'definite acute myocardial infarction' was even higher, 33·2 per cent. The 'HIP' study was a follow-up of 4·5 years of 564 male patients who survived one month after infarction. The series comprised men under 65 years of age with primary infarction, and the 4·5-year survival in the series was 81 per cent.[29] In the present study the corresponding figure for five-year survival was considerably lower, 73·9 per cent.

Several workers have noted that the mortality after the acute phase is highest during the first months.[13 14 29 33] This was the case in the present study, too. On the other hand, the mortality in this series did not decrease after the second year of follow-up, and the annual mortality during the whole follow-up period considerably exceeded that of the Helsinki population of the same age.

Age had an unfavourable effect on the five-year mortality, as has been shown in the majority of the previous studies. It has been noted, however, that the survival of younger patients with acute myocardial infarction is relatively smaller than that of older patients, if it is compared with the mortality of the general population within the same age groups.[29]

No clear differences between the sexes were found previously in the long-term survival,[13] even though not many long-term follow-up studies with large numbers of female patients with acute myocardial infarction have been published. In the present study the five-year mortality among women was lower than that among men, and age adjustment increased the difference still further. The lower mortality among women could be because a relatively larger proportion of women suffered a nontransmural infarction for, when the transmurality of infarction was standardised, there was no statistically significant differences in the mortality between men and women. Women also suffered a recurrent acute myocardial infarction somewhat less often than men. Myocardial infarction in Finland, at least in the population of working age in Helsinki, seems to be less serious in women than in men: the incidence of acute ischaemic heart disease among women is clearly lower than among men,[5] women are less prone to both sudden death and death during the first 28 days than men,[7] and their long-term mortality is clearly smaller than that of men, mainly because they tend to suffer a smaller infarction with fewer recurrences than men.

The five-year mortality among men with a transmural acute myocardial infarction was nearly double that of men with a nontransmural infarction. This probably reflects the usually smaller size of myocardial damage in nontransmural infarction compared with transmural infarction. Published reports have presented data, especially recently, which indicate that the prognosis for nontransmural infarction does not differ from that for transmural infarction, or is even poorer.[22 34–37] The series used in these studies was, however, fairly small. Both of the groups in the present study were large, though no classification into transmural or nontransmural infarction could be made for 13 per cent of the patients. Even if all these patients were in the nontransmural group, which is highly unlikely, this would not be enough to negate the considerable difference in mortality between the groups.

Conclusion

The prognosis for patients of working age in Helsinki who had an attack of acute ischaemic heart disease is poor. Only 41·6 per cent of all those 1224 patients who suffered a definite or probable acute myocardial infarction or sudden coronary death during a one-year period were alive after five years. Compared with other follow-up studies the infarctions in Helsinki seem to have a higher fatality rate than in other countries especially in the early phase,[5] but also thereafter. The exceptionally high mortality from myocardial infarction of the Finnish population of working age, especially that of men, is caused by both the high incidence and the high fatality of the disease in the acute phase, right from the first hour after the attack.

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Br Heart J 1980; **43:** 184–190

Mechanocardiographic assessment of left ventricular function in coronary artery disease*

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SUMMARY Multiple regression analysis was used in order to evaluate the independent contribution and combined use of mechanocardiographic indices for assessing cardiac function in 23 patients with coronary artery disease.

Three indices were derived from the quantitative displacement left apex cardiogram: the time from the onset of electrical depolarisation to the peak of the first derivative (t peak dD/dt) and the first derivative normalised for the amplitude of the displacement (dD/dt/D) using for D total and developed displacement. From the external carotid pulse the ratio pre-ejection period to the ejection time (PEP/LVET) was calculated. Several invasive isovolumic and ejection phase indices of left ventricular function were calculated and used as dependent variables in the multiple regression analysis. The non-invasive indices were used as dependent variables. The index dD/dt/D of the left apex cardiogram was significantly partially correlated with all invasive indices and demonstrated the highest t values. For PEP/LVET the t values were smaller and not always significant. No signficant partial correlation was found for (t peak dD/dt). The combined use of PEP/LVET and dD/dt/D resulted in a better differentiation between normal and abnormal left ventricular function.

It is concluded that quantitative apex cardiography is superior to systolic time intervals for assessing left ventricular function in coronary artery disease though both methods offer independent information and should be considered complementary.

Systolic time intervals and indices derived from the left apex cardiogram have become established methods for the non-invasive evaluation of left ventricular function in man.[1–11]

There is no general agreement as to the value of these indirect methods for assessing myocardial function at rest in patients with coronary heart disease. Moreover, it is largely unknown to which degree each of these methods independently contributes to the assessment of left ventricular function. It may be postulated that the combined use of both non-invasive methods might result in a better evaluation of left ventricular performance.

In order to clarify this problem, comparisons were made with both angiographic and isovolumic indices of contractility in a group of patients with chronic coronary artery disease. All indices, invasive and non-invasive, were obtained during the same catheterisation procedure and were correlated with each other by means of multiple linear regression analysis.

Methods

Twenty-three patients, two women and 21 men, with a mean age of 49±11 (±SD) years were selected for the study. Chronic coronary artery disease, defined as stable angina pectoris, with or without previous myocardial infarction, was present in all patients. None of them had valvular lesions. All patients had regular sinus rhythm. Informed consent was obtained before the procedure.

TECHNIQUES

A selective coronary arteriography and a left

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* Supported by a grant from the NFWO (Nationaal Fonds voor Wetenschappelijk Onderzoek), Brussels.

Received for publication 1 August 1979

ventriculogram in a 30 degree right anterior oblique position were performed in all patients. At least 15 minutes after the angiographic procedure a high-fidelity catheter tip micromanometer was introduced in the left ventricle (Telco or Millar Instruments).

Reference tracings were recorded through a side opening by means of an Elema EMT 456 strain gauge. The zero level was mid-thoracic.

The first derivative of left ventricular pressure (dP/dt) was obtained through resistance-capacitance differentiating circuits providing linear differentiation up to 45 Hz.

A calibrated displacement (D) left apex cardiogram was recorded by means of a piezoelectric crystal microphone (Elema-Schönander) with a time constant of four seconds. A description of the apparatus and the calibration procedure has been reported previously.[8 11]

The right external carotid pulse tracing was recorded by the same transducer.

Lead II of the electrocardiogram and the internal phonocardiogram, obtained by appropriate high-pass filtering from the micromanometer, were recorded simultaneously. The internal phonocardiogram was used for the determination of the onset of the high-frequency vibrations of the aortic component of the second heart sound (A2). Recordings were made on an eight-channel ink-jet recorder (Elema 81) at a paper speed of 250 mm/s. Before and after each experiment the simultaneity of the channels of the recorder was controlled.

CALCULATIONS

The following invasive indices were derived from the left ventricular pressure (LVP):

—the peak value of the first derivative of LVP: peak dP/dt (mmHg/s),

—maximum value of the ratio of the first derivative of LVP to the corresponding total pressure (P_t): $(dP/dt/P_t)$max also called Vpm,

—the linear extrapolation of this ratio to zero pressure called $VmaxP_t$,

—the ratio of the first derivative of LVP to the corresponding developed pressure (P_d = the instantaneous left ventricular pressure minus left ventricular end-diastolic pressure): $dP/dt/P_d$. The value of $dP/dt/P_d$ at the time of peak dP/dt represented $(\text{peak } dP/dt)/P_d$,

—the polynomial extrapolation of $dP/dt/P_d$ to zero pressure using P_d values > 10 mmHg was called $VmaxP_d$. As the c and k constants of the series elasticity were ignored, these indices were expressed per second.

From the left ventriculogram the following indices of myocardial function were calculated using the area-length method[12]:

—the ejection fraction (EF): the ratio of stroke volume to end-diastolic volume. In our laboratory the lower limit of normal (mean normal value minus 2 SD) for the EF was 0·64,

—the mean velocity of circumferential fibre shortening according to the method of Karliner *et al.*[13] This index is expressed in circumferences per second (circ/s).

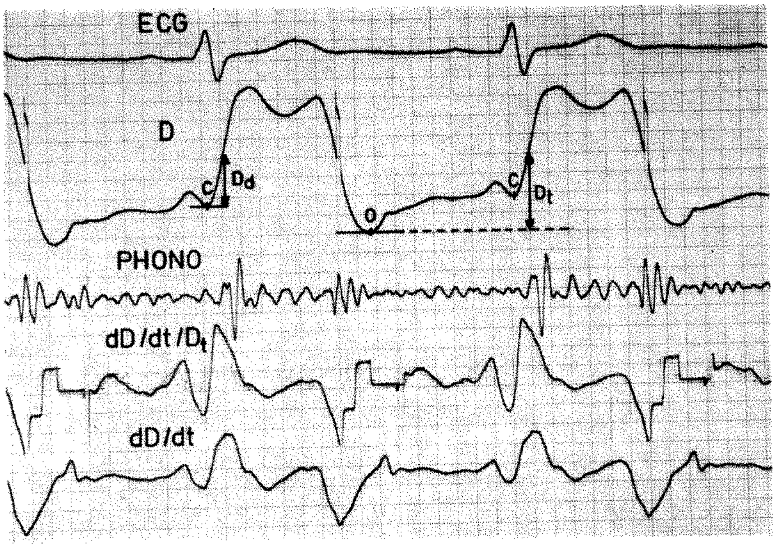

Fig. 1 *Calculation of indices of left ventricular function from the quantitative displacement left apex cardiogram (QLAC). D, apical displacement; dD/dt, first derivative of QLAC; dD/dt/D_t, normalised first derivative of QLAC using total displacement (D_t); D_d, developed displacement; C, onset of systolic rise; O, protodiastolic nadir; ECG, electrocardiogram; phono, phonocardiogram.*

Table 1 *Indices of left ventricular function (mean ± SD)*

Invasive indices	*Mean*	*±SD*	*Non-invasive indices*	*Mean*	*±SD*
Peak dP/dt (mmHg)	1466·00	567·00	t-peak dD/dt (msec)	56·83	14·96
(dP/dt/P_t)max (s^{-1})	32·01	13·06	(dD/dt/D_t)max (s^{-1})	30·05	9·85
(peak dP/dt)/P_d (s^{-1})	29·49	10·31	(peak dD/dt)/D_d (s^{-1})	32·22	9·14
Vmax P_t (s^{-1})	42·09	14·88	PEP/LVET	0·497	0·132
Vmax P_d (s^{-1})	78·27	26·05			
EF	0·511	0·207			
Mean Vcf (circ/s)	1·028	0·691			

For abbreviations of different indices see text.

The quantitative left apex cardiogram provided the non-invasive indices listed below:

—the time from the onset of electrical depolarisation to the peak value of the first derivative (t peak dD/dt), expressed in milliseconds (ms),

—the normalised first derivative of the left apex cardiogram (dD/dt/D) using for D both total (D_t) and developed (D_d) displacement. D_t is measured with the 0 point (protodiastolic nadir) and D_d with the C point (onset of systolic contraction) of the apex cardiogram as reference zero point (Fig. 1). dD/dt/D_t is calculated electronically by means of a logarithmic amplifier and differentiator and the maximum value is termed (dD/dt/D_t)max. dD/dt/D_d is measured manually and its value at the time of peak dD/dt is called (peak dD/dt)/D_d. Both indices are expressed per second.

From the right external carotid pulse tracing the ratio pre-ejection period to left ventricular ejection time, PEP/LVET, was calculated. The beginning of the upstroke of the carotid pulse was determined by extending the systolic rising and the diastolic descending limb of the preceding complex. The intersection was considered as the exact onset of the upstroke.[14] The nadir of the incisura was determined by simple inspection. PEP was measured as (Q-A_2) minus LVET, where (Q-A_2) represents the time interval from the beginning of the QRS complex to the first high-frequency vibrations of A_2.

STATISTICAL CALCULATIONS

In order to evaluate and to quantify the independent contribution of a non-invasive index, taking into account the interaction with others, multiple linear regression analysis was performed. Four non-invasive parameters were used as independent variables: (dD/dt/D_t)max, (peak dD/dt)/D_d, t peak dD/dt, and PEP/LVET. All invasive indices were successfully used as dependent variables in the regression model.

The insignificant independent variables were deleted stepwise until only significant variables remained.

Results

The mean values (±SD) of all invasive and non-invasive indices are listed in Table 1. A normal left ventricular function (EF$\geqslant$0·64 and absence of segmental contraction abnormalities) was found in seven patients.

In the multiple regression analysis the same four non-invasive indices are used as independent variables. All the invasive indices are successively used as dependent variables.

Multiple regression analysis with ejection fraction as dependent variable reveals a significant t value for (dD/dt/D_t)max and PEP/LVET. The apex cardiographic index presents the highest t value (Table 2). With peak dP/dt of the left ventricular pressure similar results are obtained (Table 3). The individual values and the single linear correlations of these indices are shown in Fig. 2 and 3. The lower limits of normal (mean normal value minus 2 SD) for (dD/dt/Dt)max,[8] PEP/LVET,[3] peak dP/dt,[15] and EF are also indicated. (dD/dt/Dt)max incorrectly categorised eight patients out of 23 and PEP/LVET incorrectly categorised six patients.

Table 2 *Multiple regression equation between ejection fraction (EF) and mechanocardiographic indices of left ventricular function (n=23)*

	t value
EF = 0·64 + 0·013 (dD/dt/D_t)max	+3·02**
− 0·003 (peak dD/dt)D_d	−0·50
− 0·001 t-peak dD/dt	−0·44
− 0·711 PEP/LVET	−2·66*
R=0·78	
= 0·50 + 0·012 (dD/dt/D_t)max	+3·92***
− 0·699 PEP/LVET	−3·12**
R=0·77***	

R=multiple correlation coefficient; n=number of patients; t=computed t value of partial correlation; *$p < 0·05$; **$p < 0·01$; ***$p < 0·001$. For other abbreviations see text.

However, an abnormality in one or two of these measurements was associated with an abnormal ejection fraction in 22 out of the 23 patients. In 11 out of 23 patients at least one non-invasive index and in nine patients both indices correctly differentiate between normal and abnormal values of peak dP/dt (Fig. 3). There is no significant linear correlation between PEP/LVET and (dD/dt/D_t)max ($r = -0{\cdot}16$ NS).

Using mean Vcf as dependent variable an independent significant contribution is found only for (dD/dt/D_t)max (Table 4). The same holds for the multiple correlation with Vpm (Table 5).

Table 6 summarises all the significant partial correlations found in the multiple regression analysis. Whether an injection phase index or an isovolumic pressure index is used as dependent variable, the normalised first derivative of the left apex cardiogram is always significantly correlated with the index under consideration and demonstrates the highest t values. The ratio PEP/LVET presents a significant partial correlation only with EF, peak dP/dt, and (peak dP/dt)/P_d. No significant partial correlation can be demonstrated for the index t peak dD/dt.

Discussion

Assessment of cardiac dynamics and myocardial function using external pulse tracings remains an important goal in non-invasive diagnostic cardiology. Among these the external carotid pulse and the left apex cardiogram are certainly the most commonly used. The apex cardiogram has been used as a substitute for pressure in timing left ventricular events,[1] [16–18] and constructing pressure dimension loops.[17] When the delay for pulse wave transmission is taken into account, the external carotid pulse closely resembles the aortic pressure.[6 14]

Table 3 *Multiple regression equation between peak value of first derivative of left ventricular pressure (peak dP/dt) and mechanocardiographic indices of left ventricular function (n=23)*

		t value
Peak dP/dt	= 687·0 + 21·7 (dD/dt/D_t)max	+1·94
	+ 22·7 (peak dD/dt/dt)/D_d	+1·46
	− 1·7 t-peak dD/dt	−0·21
	−1445·2 PEP/LVET	−2·14*
	R=0·82	
	= 805·0 + 22·9 (dD/dt/D_t)max	+2·45*
	+ 20·5 (peak dD/dt)/D_d	+1·83
	−1419·4 PEP/LVET	−2·19*
	R=0·82	
	=1444·1 + 32·5 (dD/dt/D_t)max	+3·97***
	−1958·2 PEP/LVET	−3·22**
	R=0·78***	

For abbreviations see Table 2.

Table 4 *Multiple regression equation between mean velocity of circumferential fibre shortening (mean Vcf) of left ventricle and mechanocardiographic indices of left ventricular function (n=23)*

		t value
Mean Vcf	= 1·27 + 0·051 (dD/dt/D_t)max	+2·93**
	− 0·022 (peak dD/dt)/D_d	−0·90
	− 0·007 t-peak dD/dt	−0·54
	− 1·400 PEP/LVET	−1·32
	R=0·67	
	= 0·80 +0·046 (dD/dt/D_t)max	+3·14**
	− 0·013 (peak dD/dt)/D_d	−0·73
	− 1·503 PEP/LVET	−1·47
	R=0·66	
	= 0·39 + 0·044 (dD/dt/D_t)max	+3·34**
	− 0·001 PEP/LVET	−1·29
	R=0·65	
	=−0·26 + 0·043 (dD/dt/D_t)max	+3·55**
	r=0·61**	

For abbreviations see Table 2.

Morphological changes of these tracings already offer many diagnostic possibilities as to valvular lesions and cardiac performance. Both tracings also provide a quantitative estimate of left ventricular function. Both methods, however, also have their limitations: for the left apex cardiogram, the absence of a true zero level and a still incomplete understanding of the determinants of its time course and morphology; for systolic time intervals, the change in opposite direction of some determinants of these intervals during changes in the inotropic state of the heart.[19]

The time interval from the onset of electrical depolarisation to the peak of the first derivative of the left apex cardiogram has been proposed as a quantitative index in assessing left ventricular function on the apex cardiogram.[2 20] Subsequently the concept of 'amplitude normalisation' was introduced. It was found that the left ventricular pressure plays a predominant role in shaping the morphology of the left apex cardiogram[21] and that a distinct similarity in slope exists between the left apex cardiogram and the left ventricular pressure during isovolumic contraction.[7] In view of these findings the left apex cardiogram was calibrated and its first derivative was normalised for the amplitude of the apical impulse. Recent studies from our laboratory demonstrated the clinical value and advantages of the calibrated apex cardiogram and its normalised first derivative.[8 11]

Several authors have correlated systolic time intervals with other measurements of cardiac performances.[3 4 6 9] The index PEP/LVET is used

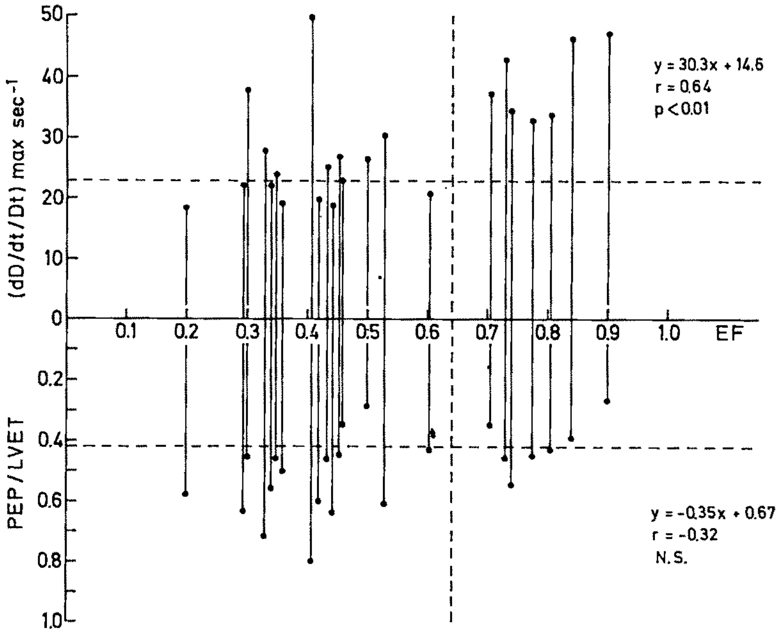

Fig. 2 *Individual values and single linear correlations of ejection fraction (EF), ratio pre-ejection period/ejection time (PEP/LVET), and normalised first derivative of apex cardiogram (dD/dt/Dt) max. Dotted lines indicate lower limits of normal.*

and Garrard *et al.*[4] have shown the highest correlation coefficient with the angiographic ejection fraction (r= −0·90). In the latter study various forms of heart disease were included, with extreme values for ejection fraction (ranging from 0·08 to 0·84). When, however, it was applied to patients with coronary artery disease the correlation coefficients were smaller.[9 22 23]

At present there is no single undisputed invasive index for assessing myocardial contractility in man. Both isovolumic and ejection phase indices of contractility are susceptible to criticism and have their advantages and limitations.[24 25] In order to evaluate the usefulness and the relative importance of calibrated apex cardiography and systolic time intervals for assessing left ventricular function in coronary artery disease, comparisons were made with both invasive methods. Multiple linear

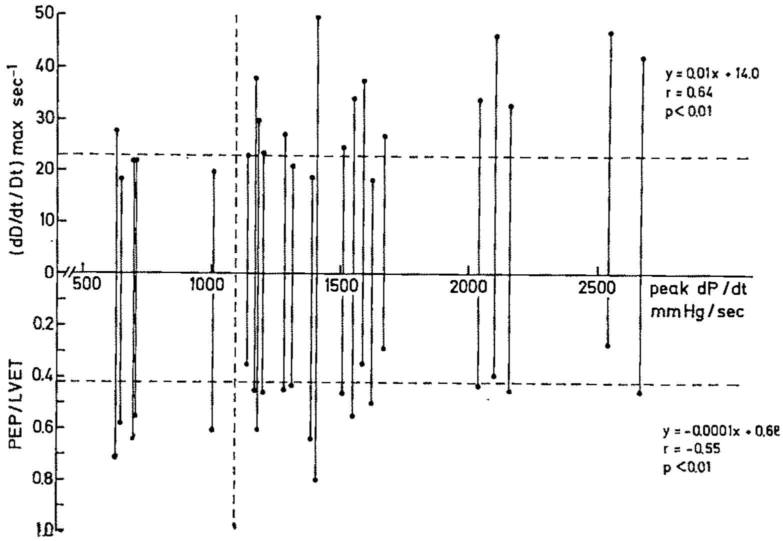

Fig. 3 *Individual values and single linear correlations of peak value of first derivative left ventricular pressure (peak dP/dt), ratio pre-ejection period/ejection time (PEP/LVET), and normalised first derivative of apex cardiogram (dD/dt/Dt)max. Dotted lines indicate lower limits of normal.*

Table 5 *Multiple regression equation between peak measured velocity of shortening of contractile elements (Vpm) and mechanocardiographic indices of left ventricular function (n=23)*

	t value
Vpm = 37·74 + 1·20 (dD/dt/D_t)max	+4·21***
− 0·60 (peak dD/dt)D_d	−1·50
− 0·18 t-peak dD/dt	−0·90
− 24·75 PEP/LVET	−1·43
R=0·77	
= 25·03 + 1·07 (dD/dt/D_t)max	+4·38***
− 0·36 (peak dD/dt)/D_d	−1·22
− 27·53 PEP/LVET	−1·63
R=0·76	
= 13·88 + 0·90 (dD/dt/D_t)max	+4·42***
− 18·13 PEP/LVET	−1·19
R=0·73	
= 3·67 + 0·94 (dD/dt/D_t)max	+4·63***
r=0·71	

For abbreviations see Table 2.

regression analysis was used to quantify the individual independent contribution of each non-invasive index.

Table 6 *Multiple regression analysis between invasive and non-invasive indices of left ventricular function in patients with chronic coronary artery disease (n=23)*

Dependent variables	*Independent variables*				*Correlation coefficient (R, r)*
	(dD/dt/D_t)max	*(peak dD/dt)/D_d*	*t peak dD/dt*	*PEP/LVET*	
EF	***			**	0·77***
Mean Vcf	**				0·61**
(dP/dt/P_t) max or Vpm	***				0·71***
Vmax P_t	**				0·62**
peak dP/dt	***			**	0·78***
(peak dP/dt)/P_d		***		*	0·83***
Vmax P_d		**			0·57**

*p < 0·05; **p < 0·01; ***p < 0·001. For abbreviations of different indices see text.

From the statistical results it is clear that most important indirect information on left ventricular function is provided by the normalised derivative of the apex cardiogram. This is true whether angiographic or pressure indices of cardiac performance are used as dependent variables. When developed pressure is used in the calculation of the isovolumic indices, the corresponding apex cardiographic indices based on developed displacement are involved, since the 0-C amplitude of the left apex cardiogram reflects left ventricular end-diastolic pressure.[16] Furthermore, the concept of normalisation of the first derivative, also termed 'normalised velocity', can be considered as a general index for assessing cardiac performance, equally applicable to invasive and non-invasive methods.[11] [26]

The ratio PEP/LVET also provides independent significant information, as shown by the regression equation with the EF and peak dP/dt of the left ventricular pressure. It should be noted that the present investigations were limited to resting frequencies. Though better identification of abnormal cardiac function in coronary artery disease during exercise is reported using systolic time intervals,[22] [27] the overall correlations with invasively determined indices of cardiac performance have improved only a little.[22]

It is noteworthy that in this group of patients and with this regression model, no significant independent information on left ventricular function is provided by the index t peak dD/dt. The most logical explanation appears to be that the pre-ejection period and the normalised first derivative of the left apex cardiogram already contain most of the information provided by this index.

From our data it can be concluded that quantitative apex cardiography is a useful non-invasive tool for the evaluation of cardiac function in patients with coronary artery disease. In the group of patients studied, it is superior to systolic time intervals.

Although each method alone is not a strong indication of the state of the left ventricle in chronic coronary artery disease, both methods contain useful independent information and should be used together.

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Br Heart J 1980; **43**: 191–198

Bypass surgery for left main coronary artery disease

Reduced perioperative myocardial infarction with preoperative intra-aortic balloon counterpulsation[*]

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SUMMARY From July 1975 to December 1977, 91 consecutive patients with left main coronary artery disease defined by cardiac catheterisation as ≥50 per cent luminal narrowing underwent coronary bypass surgery. Prospective examination of the preoperative and postoperative clinical course of these patients was performed to determine the incidence of perioperative myocardial infarction. Intra-aortic balloon counterpulsation was instituted preoperatively in 35 patients, and these patients were classed as group A. Fifty-six patients did not receive the intra-aortic balloon pump and were classed as group B. Of 26 demographic, clinical, haemodynamic, and operative descriptors, only two were found to be significantly different between the two groups: the severity and the pattern of angina. Group A had a higher percentage of patients with class IV angina (80% vs 45%) and a greater proportion with unstable angina (37% vs 7%). Despite these differences group A patients had only a 3 per cent incidence of perioperative myocardial infarction while group B had a 23 per cent perioperative infarction rate. It is suggested that perioperative intra-aortic balloon counterpulsation can reduce the risk of perioperative myocardial infarction in patients with left main coronary artery stenosis.

Obstructive lesions involving the left main coronary artery have been associated with a guarded prognosis in patients with ischaemic heart disease.[1–3] Early surgical intervention has become increasingly common for this disease, and many centres have reported a substantial relief of symptoms after operation.[4–6] Furthermore, in comparing medical and surgical treatment for patients with left main stenosis several studies indicate a prolonged survival in surgically treated groups.[5–7]

Left main disease is itself a significant risk factor for operative mortality and perioperative myocardial infarction in coronary bypass surgery. Operative mortality has been reported to be two- to fivefold higher and perioperative myocardial infarction over 50 per cent more common in patients with significant left main narrowing.[3 6 8]

Experience with prophylactic and therapeutic intra-aortic balloon counterpulsation has shown it to be of value for patients with serious left ventricular dysfunction, impending myocardial infarction, or both, who were undergoing cardiac surgery.[9–11] Evaluation of the prophylactic use of the intra-aortic balloon pump for patients undergoing bypass grafting for left main disease comprises the subject of this report. We collected data retrospectively[12] on 91 consecutive patients undergoing bypass surgery for left main coronary obstruction from July 1975 to December 1977 to determine prospectively if preoperative intra-aortic balloon pumping had any effect on the incidence of perioperative myocardial infarction.

Patients and methods

Data were collected on 91 consecutive patients shown to have greater than 50 per cent obstruction of the left main coronary artery who underwent aortocoronary bypass grafting at Yale-New Haven Hospital from July 1975 to December 1977.

Diagnostic cardiac catheterisation consisted of pressure measurements, cardiac output determination, right anterior oblique left ventriculogram for

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[*] This study was supported in part by a Yale University fluid grant.

Received for publication 16 October 1979

analysis of regional wall motion,[13] mitral regurgitation, and ejection fraction (calculated according to the method of Greene *et al.*),[11] and selective coronary cinearteriography, all performed by standard techniques. A greater than 50 per cent stenosis of the left main coronary artery and a greater than 70 per cent stenosis for other coronary arteries was considered significant.

Coronary bypass surgery was performed within two weeks after angiography in all patients. All grafts to the left circumflex and right coronary arteries were performed using reversed autogenous saphenous veins. The left anterior descending artery was grafted using the left internal mammary artery in 37 patients, aortosaphenous bypass grafts in 45 patients, and double grafts using aortosaphenous vein grafts and the left internal mammary artery in nine patients. Dissection of the left internal mammary artery from the chest wall and proximal anastomoses of saphenous vein grafts were accomplished without cardiopulmonary bypass. Distal anastomoses were performed on full cardiopulmonary bypass with the heart in ventricular fibrillation, and aortic cross-clamping was used only when a dry field could not be obtained by local occlusion of the coronary artery. Each distal anastomosis was probed near its completion to ensure that the anastomotic communication was wider than the grafted coronary artery. The left ventricle was vented in all patients by a catheter passed through the right superior pulmonary vein or the ventricular apex into the left ventricular cavity. All blood aspirated into the extracorporeal circuit from the vent or cardiac suction lines was filtered through a millipore filter* before being returned to the oxygenator.† Whole blood was transfused only if perfusate haematocrit fell below 25 per cent, and serum potassium levels were carefully monitored and appropriately adjusted.

DEFINITION OF VARIABLE STUDIES

Perioperative myocardial infarction was defined as myocardial necrosis occurring within one week postoperatively and identified by serial electrocardiograms, necropsy, or both. All patients had daily standard 12 lead electrocardiograms from the day before operation until the seventh postoperative day with the first postoperative tracing obtained upon arrival in the surgical intensive care unit. Routine precautions were taken to ensure that praecordial electrocardiographic leads were recorded from the same praecordial place before and after operation. The criterion for acute myocardial infarction was the development on serial electrocardiograms of new significant pathological Q waves, equivalent to class I-1 and I-2 of the Minnesota Code.[15] These new Q waves were considered diagnostic of myocardial infarction if they were recorded from completely different sites from preoperative myocardial infarctions. New intraventricular conduction defects, new bundle-branch blocks, increasing size of previous Q waves, and ST segment or T wave changes without new pathological Q waves were not considered diagnostic of myocardial infarctions. Rises in serum creatine kinase (CK), serum aspartate transaminase (AST), and CK-MB isoenzyme were not considered diagnostic of myocardial infarction. Mortality of perioperative myocardial infarction was considered to be death up to four weeks after coronary surgery.

STATISTICAL METHODS

Contingency table χ^2 and multiple logistic regression model were used to analyse the data.[16] A probability value less than 0·05 was considered statistically significant. When information on a specific clinical characteristic of a patient was not available, that patient was excluded from analysis of the particular variable.

PATIENT GROUPINGS

Thirty-five patients were treated preoperatively with intra-aortic balloon counterpulsation,‡ and these patients were classed in this study as group A. Fifty-six patients did not receive the intra-aortic balloon pump and were classed as group B. The individual clinical decision regarding the insertion of a pump depended largely upon its availability, but maximal effort was made to assist patients with unstable angina with counterpulsation. When used, the intra-aortic balloon pump was introduced under local anaesthesia in the surgical intensive care unit through the common femoral artery via an end-to-side 10 mm 'dacron' graft and advanced into the descending thoracic aorta. When difficulties were encountered or anticipated, a wire-guided central lumen balloon catheter[17] was introduced under direct fluoroscopy and pressure monitoring in the cardiac catheterisation laboratory. Details of introduction and management of the intra-aortic balloon pump have been previously described.[18]

In group A patients the balloon pump was inserted before cardiac catheterisation and operation in 18, and before operation in 17. It was removed either at bypass surgery or up to 48 hours postoperatively in the surgical intensive care unit in all cases. In no instance was the intra-aortic balloon pump left on longer than seven days (average four days).

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* Swank Micro-emboli Filter, Pioneer Filter Co, Beaverton, Oregon.

† Temptrol Disposable Blood Oxygenator Model Q100, Bentley Laboratories Inc., Santa Anna, California; or Kolobine Disposable Membrane Ogygenator, Sci-Med, Minneapolis, Minnesota.

‡ Avco Intra-aortic Balloon, Hoffman-LaRoche Inc., Cranbury, New Jersey.

DEMOGRAPHIC CHARACTERISTICS

Table 1 displays variables relating to the past medical history and physical examination of this group of 91 patients with left main stenosis. It can be seen that the following variables were distributed approximately equally between the 35 group A and 56 group B patients: age over 55, sex, history of previous myocardial infarction, history of congestive heart failure, positive family history (ischaemic heart disease in immediate family member before age 55), evidence of peripheral vascular disease, history of smoking, and propranolol dosage and tapering. Sixty-three per cent of the population was over age 55; 80 per cent were male; 43 per cent had a history of previous myocardial infarction; 28 per cent had symptoms of congestive heart failure; 62 per cent had a positive family history; 26 per cent showed signs of peripheral vascular disease; 64 per cent had a positive smoking history; 60 per cent had been on more than 160 mg propranolol per day, and 8 per cent had propranolol therapy abruptly stopped without tapering before operation.

Statistically significant differences between the two groups were found in three of the studied demographic descriptors: severity of angina pectoris, pattern of angina pectoris, and use of propranolol before surgery for control or attempted control of symptoms. Eighty per cent of group A patients had New York Heart Association (NYHA) class IV angina while only 45 per cent of group B patients had class IV symptoms ($p < 0{\cdot}05$). Unstable angina (defined as constant chest pain at rest of at least 20 minutes' duration, refractory to medical therapy with beta-blockers and nitrates) was present in 37 per cent of group A patients compared with 7 per cent of group B patients ($p < 0{\cdot}05$). Propranolol was used before admission for operation in 97 per cent of group A patients compared with 76 per cent of those in group B ($p < 0{\cdot}02$). Of note is that there was no significant difference in method of cessation of propranolol therapy among patients receiving the beta-blocker in the two groups. These three demographic indices outline, then, a group A population with clinically more severe angina pectoris than group B.

Similarly, radiological, haemodynamic, and angiographic data are shown in Table 2. A comparable distribution between the two groups can be seen for cardiac enlargement (CT ratio >50%), abnormal ejection fraction, raised left ventricular end-diagstolic pressure (LVEDP), evidence of mitral regurgitation, and presence of triple vessel disease and of abnormal segmental wall motion. Eighteen per

Table 1 *Demographic characteristics: medical history and physical examination*

		Total	*Group A (IABP)*	*Group B (no IABP)*	*p value*
Number of patients		91	35	56	
Age (y)					
<55		34/91 (37%)	10/35 (29%)	24/56 (43%)	NS
⩾55		57/91 (63%)	25/35 (71%)	32/56 (57%)	NS
Sex					
M		73/91 (80%)	31/35 (89%)	42/56 (75%)	NS
F		18/91 (20%)	4/35 (11%)	14/56 (25%)	NS
Previous myocardial infarction		37/87 (43%)	16/35 (46%)	21/52 (40%)	NS
History of congestive heart failure		24/87 (28%)	10/35 (29%)	14/52 (27%)	NS
+Family history		54/87 (62%)	22/33 (67%)	32/54 (59%)	NS
History of hypertension		29/90 (32%)	10/35 (29%)	19/55 (35%)	NS
Peripheral vascular disease		24/91 (26%)	7/35 (20%)	17/56 (30%)	NS
Smoking		58/90 (64%)	21/34 (62%)	37/56 (66%)	NS
Angina					
Severity:	Class I (NYHA)	2/91 (1%)	0/35 (0%)	2/56 (3%)	NS
	Class II	14/91 (15%)	3/35 (9%)	11/56 (20%)	NS
	Class III	22/91 (24%)	4/35 (11%)	18/56 (32%)	NS
	Class IV	53/91 (58%)	28/35 (80%)	25/56 (45%)	<0·05
Pattern:	Stable	22/91 (24%)	6/35 (17%)	16/56 (29%)	NS
	Progressive	52/91 (57%)	16/35 (46%)	36/56 (64%)	NS
	Unstable	17/91 (19%)	13/35 (37%)	4/56 (7%)	<0·05
Propranolol					
None		14/89 (16%)	1/35 (3%)	13/54 (24%)	<0·02
<160 mg daily		22/89 (25%)	6/35 (17%)	16/54 (30%)	NS
⩾160 mg daily		53/89 (60%)	28/35 (80%)	25/54 (46%)	NS
Propranolol tapering					
No propranolol		14/75 (19%)	1/35 (3%)	13/40 (32%)	<0·01
Abrupt withdrawal		6/75 (8%)	1/35 (3%)	5/40 (12%)	NS
Tapered or discontinued 48 hours before operation		53/75 (71%)	33/35 (94%)	22/40 (55%)	NS

IABP, intra-aortic balloon pump.

Table 2 *Demographic characteristics: chest x-ray and cardiac catheterisation*

	Total	*Group A (IABP)*	*Group B (no IABP)*	*p value*
Cardiac enlargement	16/91 (18%)	6/35 (17%)	10/56 (18%)	NS
Vessels diseased				
LMCA only	14/91 (15%)	2/35 (6%)	12/56 (21%)	NS
LMCA+RCA	77/91 (85%)	33/35 (94%)	44/56 (79%)	NS
Ejection fraction				
⩾0·60	39/75 (52%)	14/29 (48%)	25/46 (54%)	NS
<0·60	36/75 (48%)	15/29 (52%)	21/46 (46%)	NS
LVEDP				
⩽12 mmHg	31/84 (37%)	11/34 (32%)	20/50 (40%)	NS
>12 mmHg	53/84 (63%)	23/34 (68%)	30/50 (60%)	NS
Mitral regurgitation	6/81 (7%)	2/35 (6%)	4/46 (9%)	NS
Abnormal segmental wall motion	53/84 (63%)	25/34 (73%)	28/50 (56%)	NS

LMCA, left main coronary artery; LVEDP, left ventricular end-diastolic pressure; RCA, right coronary artery.

cent of the total population had cardiac enlargement; 48 per cent had an ejection fraction of less than 0·60; 63 per cent had LVEDP of greater than 12 mmHg; 7 per cent had evidence of mitral regurgitation; 85 per cent had disease of the right coronary artery (RCA) in addition to the left system; and 63 per cent had abnormal segmental wall motion on left ventriculogram.

Table 3 displays operative data for the group. An approximately equal distribution of patients receiving the intra-aortic balloon pump and those not was seen for number of major diseased vessels not grafted (incomplete revascularisation), cardiopulmonary bypass time, anoxia time (aortic cross-clamping), and number of grafted vessels. Sixty-seven per cent of the population had complete revascularisation; 58 per cent had a cardiopulmonary bypass time longer than 90 minutes; 41 per cent had anoxia times of greater than 30 minutes; and 69 per cent received three or more grafts. No differences in operative indices were seen between the two groups.

Results

Perioperative myocardial infarction occurred in 15 per cent of the total population of 91 patients with left main disease. An analysis of incidence of perioperative myocardial infarction for previously reported or suggested risk factors is displayed in Table 4. We found no significant association between perioperative myocardial infarction and age over 55, sex, severity or pattern of anginal pain, the presurgical use of beta-blockers, dosage of propranolol if used, method of propranolol discontinuation, cardiac enlargement, mitral regurgitation, abnormal segmental wall motion, abnormal ejection fraction, raised LVEDP, anoxia time, disease of the right coronary artery, or incomplete revascularisation. A significant association was seen, however, between cardiopulmonary bypass time greater than 90 minutes ($p < 0{\cdot}05$) and suggested for more than three grafts performed ($p < 0{\cdot}10$). Twenty-three per cent of patients with cardiopulmonary bypass times of longer than 90 minutes infarcted compared

Table 3 *Operative history*

	Total	*Group A (IABP)*	*Group B (no IABP)*	*p value*
Number of grafts performed				
1	1/91 (1%)	0/35 (0%)	1/56 (2%)	NS
2	26/91 (29%)	4/35 (11%)	22/56 (39%)	NS
3	56/91 (62%)	26/35 (74%)	30/56 (54%)	NS
⩾4	7/91 (8%)	4/35 (11%)	3/56 (5%)	NS
Diseased vessels not grafted				
None	61/91 (67%)	24/35 (69%)	37/56 (66%)	NS
LAD	2/91 (2%)	1/35 (3%)	1/56 (2%)	NS
LCF	21/91 (23%)	6/35 (17%)	15/56 (27%)	NS
RCA	7/91 (8%)	4/35 (11%)	3/56 (5%)	NS
Cardiopulmonary bypass time				
⩽90 seconds	38/91 (42%)	13/35 (37%)	25/56 (45%)	NS
>90 seconds	53/91 (58%)	22/35 (63%)	31/56 (55%)	NS
Anoxia time				
0	27/91 (30%)	11/35 (31%)	16/56 (29%)	NS
0–30 seconds	27/91 (30%)	8/35 (23%)	19/56 (34%)	NS
31–60 seconds	30/91 (33%)	11/35 (31%)	19/56 (34%)	NS
>60 seconds	7/91 (8%)	5/35 (14%)	2/56 (4%)	NS

I ABP, intra-aortic balloon pump; LAD, left anterior descending coronary artery; LCF, circumflex coronary artery; RCA, right coronary artery.

Table 4 *Patients sustaining perioperative myocardial infarctions*

	Total	*Group A (IABP)*	*Group B (no IABP)*	*p value*
Incidence	14/91 (15%)	1/35 (3%)	13/56 (23%)	<0·05
Age (y)				
<55	5/34 (15%)	0/10 (0%)	5/24 (21%)	NS
⩾55	9/57 (16%)	1/25 (4%)	8/32 (25%)	NS
Sex				
M	11/73 (15%)	1/31 (3%)	10/42 (24%)	NS
F	3/18 (17%)	0/4 (0%)	3/14 (21%)	NS
Angina				
Severity: Class I (NYHA)	0/2 (0%)	—	0/2 (0%)	NS
Class II	4/14 (29%)	0/3 (0%)	4/11 (36%)	NS
Class III	3/22 (14%)	0/4 (0%)	3/18 (17%)	NS
Class IV	7/53 (13%)	1/28 (4%)	6/25 (24%)	NS
Pattern: Stable	5/22 (23%)	0/6 (0%)	5/16 (31%)	NS
Progressive	8/52 (15%)	1/16 (6%)	7/36 (19%)	NS
Unstable	1/17 (6%)	0/13 (0%)	1/4 (25%)	NS
Propranolol				
None	4/14 (29%)	0/1 (0%)	4/13 (31%)	NS
< 160 mg daily	3/22 (14%)	0/6 (0%)	3/16 (19%)	NS
⩾160 mg daily	7/53 (13%)	1/28 (4%)	6/25 (24%)	NS
Propranolol tapering				
No propranolol	4/14 (29%)	0/1 (0%)	4/13 (31%)	NS
Abrupt withdrawal	0/6 (0%)	0/1 (0%)	0/5 (0%)	NS
Tapered or discontinued on IABP 36 hours before operation	7/55 (13%)	1/33 (3%)	6/22 (27%)	NS
Cardiac enlargement	0/16 (0%)	0/6 (0%)	0/10 (0%)	NS
Mitral regurgitation	0/6 (0%)	0/2 (0%)	0/4 (0%)	NS
Abnormal segmental wall motion	6/53 (11%)	1/25 (4%)	5/28 (18%)	NS
Ejection fraction				
⩾0·60	7/39 (18%)	1/14 (7%)	6/25 (24%)	NS
<0·60	5/36 (14%)	0·15 (0%)	5/21 (24%)	NS
LVEDP				
⩽12	6/31 (19%)	1/11 (9%)	5/20 (25%)	NS
> 12	7/53 (13%)	0/23 (0%)	7/30 (23%)	NS
Cardiopulmonary bypass time				
⩽90 seconds	2/38 (5%)	0/13 (0%)	2/25 (8%)	NS
> 90 seconds	12/53 (23%)	1/22 (5%)	11/31 (35%)	<0·05
Anoxia time				
0	3/27 (11%)	0/11 (0%)	3/16 (19%)	NS
0–30 seconds	4/27 (15%)	1/8 (13%)	3/19 (16%)	NS
31–60 seconds	6/30 (20%)	0/11 (0%)	6/19 (32%)	NS
> 60 seconds	1/7 (14%)	0·5 (0%)	1/2 (50%)	NS
Vessels diseased				
LMCA (RCA normal)	1/14 (7%)	0/2 (0%)	1/12 (8%)	NS
LMCA+RCA	13/77 (17%)	1/33 (3%)	12/44 (27%)	<0·05
Number of grafts performed				
1	0/1 (0%)	—	0/1 (0%)	NS
2	5/26 (19%)	1/4 (25%)	4/22 (18%)	NS
3	7/56 (12%)	0/26 (0%)	7/30 (23%)	<0·05
⩾4	2/7 (29%)	0/4 (0%)	2/3 (67%)	NS
Diseased vessels not grafted				
All grafted	9/61 (15%)	0/24 (0%)	9/37 (24%)	<0·05
One diseased vessel not grafted	5/30 (17%)	1/11 (9%)	4/19 (21%)	NS
Specifically: LAD	1/2 (50%)	0/1 (0%)	1/1 (100%)	NS
LCF	3/21 (14%)	1/6 (17%)	2/15 (13%)	NS
RCA	1/7 (14%)	0/4 (0%)	1/3 (33%)	NS
Location of infarcts:				
Anterior	1	0	1	
Lateral	3	1	2	
Posterior	3	0	3	
Inferior	7	0	7	

LAD, left anterior descending; LCF, circumflex coronary artery; LMCA, left main coronary artery; LVEDP, left ventricular end-diastolic pressure; RCA, right coronary artery.

with only 5 per cent of those with cardiopulmonary bypass times of less than 90 minutes. Twenty-nine per cent of patients receiving four or more grafts infarcted compared with 12 per cent with less than four grafts.

In the intra-aortic balloon pump group (group A) only one patient infarcted (1/35, 3%) perioperatively compared with 13 in the group not receiving the balloon pump (13/56, 23%), $p<0.05$. We ran a similar analysis of reported risk factors for perioperative myocardial infarction against the results in each group. As with the total population, both groups showed an association of perioperative myocardial infarction with cardiopulmonary bypass times of greater than 90 minutes ($p < 0\cdot05$). In group B, more than three grafts performed was a suggested risk for perioperative myocardial infarction (67% vs 23%, $p < 0\cdot05$) as was the presence of triple vessel disease (27% vs 8%, $p < 0\cdot05$).

Statistical analysis of the interdependence of risk factors was performed to determine if any combination was additive. Table 5 displays data showing an additive effect for the combination of triple vessel disease and not using the intra-aortic balloon pump and for the combination of cardiopulmonary bypass times longer than 90 minutes and not using the intra-aortic balloon pump. The incidence of perioperative myocardial infarction in triple vessel disease and not using the intra-aortic balloon pump was 27 per cent while the absence of triple vessel disease and using the balloon yielded a nil infarction rate ($p < 0\cdot05$). Similarly, perioperative myocardial infarction was seen in 35 per cent of patients with prolonged cardiopulmonary bypass times not using the intra-aortic balloon pump compared with none with shorter cardiopulmonary bypass times using the balloon ($p < 0\cdot05$). Other combinations of risk factors did not show a significant additive relation to perioperative myocardial infarction.

The overall mortality in this operated series in patients with left main coronary stenoses was 8·7 per cent (8/91). The mortality of perioperative myocardial infarction in this study was 36 per cent (5/14) while patients not sustaining a myocardial infarction had an operative mortality of 3·9 per cent (3/77). Of the three patients who died in the non-infarcted population, one was in group A and two were in group B. All three patients died as a result of left ventricular failure but there was no evidence of perioperative myocardial infarction either by electrocardiographic criteria or by necropsy.

In addition to the 35 successful preoperative insertions of the intra-aortic balloon pump there were four unsuccessful attempts and nine successful intra- or postoperative placements. In three of the unsuccessful attempts the intra-aortic balloon pump could not be advanced beyond the bifurcation of the abdominal aorta and was withdrawn without complication. The fourth led to an aortic dissection that healed without surgical intervention. There were two postoperative groin infections, and no cases of arterial insufficiency. The overall complication rate was 6 per cent, 3/48 (Table 6).

Discussion

In this study we report on 91 consecutive patients with left main coronary artery disease undergoing bypass surgery. Thirty-five patients received the intra-aortic balloon pump preoperatively and 56 did not. Statistically significant differences between the two groups among 26 demographic, clinical, haemodynamic, and operative descriptors were found only in the severity of angina pectoris, pattern of angina pectoris, and presurgical use of beta-blockers. These three indices outlined the group receiving the intra-aortic balloon pump as consisting of a higher percentage of patients with more severe anginal symptoms.

Perioperative myocardial infarction occurred in 15 per cent of the overall sample using very stringent Q wave electrocardiographic criteria. This is comparable to previously reported series in which the incidence of perioperative myocardial infarction ranged from 10·7 to 37·5 per cent.[6 19 20] It is likely that this report underestimates the true incidence of perioperative myocardial infarction, since the rigid electrocardiographic criteria employed exclude a significant number of patients with possible, but less striking evidence of myocardial necrosis. In particular, patients sustaining non-transmural myocardial damage would probably be excluded by our criteria, as well as those sustaining transmural lesions in such sites that electrocardiographic changes were obscured by previous infarctions. Furthermore, while transient or permanent intraventricular conduction abnormalities might suggest myocardial damage, we did not consider these changes conclusive evidence for infarction. The use of serial serum enzyme determinations was

Table 5 *Perioperative myocardial infarction*

	Patients with IABP	*Patients without IABP*	*p value*
Vessels diseased			
LMCA only	0/2 (0%)	1/12 (8%)	NS
LMCA+RCA	1/33 (3%)	12/44 (27%)	<0·05
CPB time			
⩽90 seconds	0/13 (0%)	2/25 (8%)	NS
>90 seconds	1/22 (5%)	11/31 (35%)	<0·05

CPB, cardiopulmonary bypass time; IABP, intra-aortic balloon pump; LMCA, left main coronary artery; RCA, right coronary artery.

Table 6 *Complications of intra-aortic balloon placement or attempted placement*

Intra-aortic balloon pump insertion	
Before operation	35—Group A
During or after operation	9 Group B
Unsuccessful attempts	4
Total	48
Complications	
Infection (groin or sepsis)	2/48 (4%)
Aortic dissection	1/48 (2%)
Arterial insufficiency	0/48 (0%)
Overall	3/48 (6%)

felt to be an unreliable method for determining perioperative infarction, as serum CK and AST levels are raised during surgery by musculoskeletal trauma,[21] and CK-MB isoenzyme measurements have been shown to overestimate the incidence of perioperative myocardial infarction after bypass surgery.[22]

No correlation was found between infarction and preoperative clinical presentation, haemodynamic factors such as raised LVEDP or abnormal ejection fraction, abnormalities of contraction, or correlation to additional disease of the right coronary artery. There was also no association with incomplete revascularisation or time of aortic cross-clamping. A significant association of perioperative myocardial infarction was found in patients with prolonged cardiopulmonary bypass times and suggested for more than three grafts performed. However, it is difficult to draw conclusions regarding the importance of multiple grafts, because of the few patients in our series having more than three grafts. Several investigators have found bypass time and number of grafts performed to be related to the frequency of perioperative myocardial infarction.[8 19 23] We recognise, however, that cardiopulmonary bypass times of longer than 90 minutes are frequently associated with technically difficult anastomoses between the graft and extensively diseased vessels. Our series differed from the results of Brewer *et al.*[19] but concurred with others[8 23] in that severity and pattern of anginal pain were not related to the frequency of perioperative myocardial infarction in the overall group. We also found no correlation of perioperative myocardial infarction to the number of diseased vessels or to incomplete revascularisation, in contrast to previous reports.[19 20] We feel that some of these differences may well be related to the beneficial effects of the intra-aortic balloon pump as analysis of patients without the pump suggests more parallels to previously reported results.

While group A (intra-aortic balloon pump) had a greater proportion of patients with more severe clinical presentation, we found this group to have a significantly lower incidence of perioperative myocardial infarction than group B (3% vs 23%, $p < 0{\cdot}05$). Feola and colleagues reported a similar reduction in incidence of perioperative myocardial infarction using the intra-aortic balloon pump before bypass surgery in patients with poor left ventricular function.[10] They found a 30·4 per cent perioperative myocardial infarction rate in the group not assisted with preoperative counterpulsation and only 4 per cent in the assisted group.

Statistical analysis of combinations of risk factors for patients with left main disease showed a significantly additive risk for perioperative myocardial infarction when the intra-aortic balloon pump was not used in the presence of disease of the right coronary artery. A similar additive risk was seen when the pump was not used and the cardiopulmonary bypass time prolonged.

The mortality of myocardial infarction was 36 per cent in this series, while patients not sustaining perioperative infarction had a mortality of 3·9 per cent. This high rate shows the malignant nature of infarction for patients with left main disease and is in accord with recent reports.[23–25]

Of 48 attempts at introduction of an intra-aortic balloon pump there were three complications: one aortic dissection that healed without operation and two groin infections. No patient in the intra-aortic balloon pump group suffered peripheral vascular disease as a result of this procedure. This is comparable with the experience of several investigators who have reported a 0 to 17 per cent overall complication rate and a 0 to 15 per cent rate of arterial insufficiency after balloon placement.[26–29]

Our results suggest that the risk of perioperative infarction can be reduced by the preoperative institution of intra-aortic balloon counterpulsation in patients with left main disease undergoing bypass surgery. Even in the clinical setting of mild symptoms and normal or near normal haemodynamics, the perioperative infarction rate is high, and careful preoperative intra-aortic balloon pump introduction can be of significant benefit.

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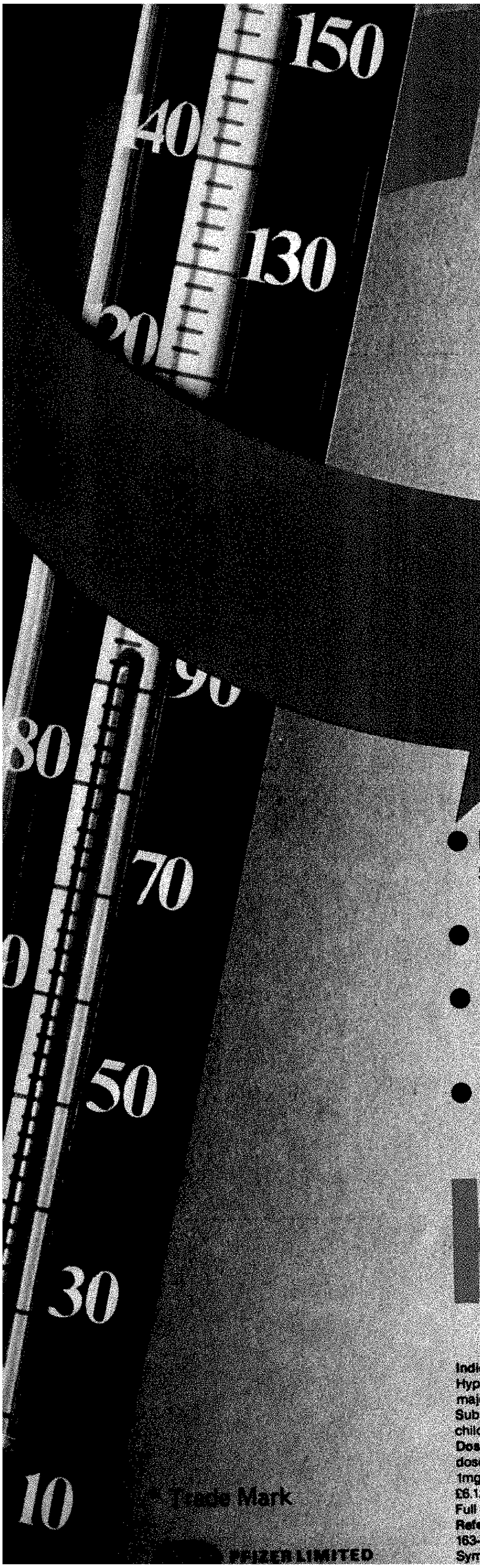

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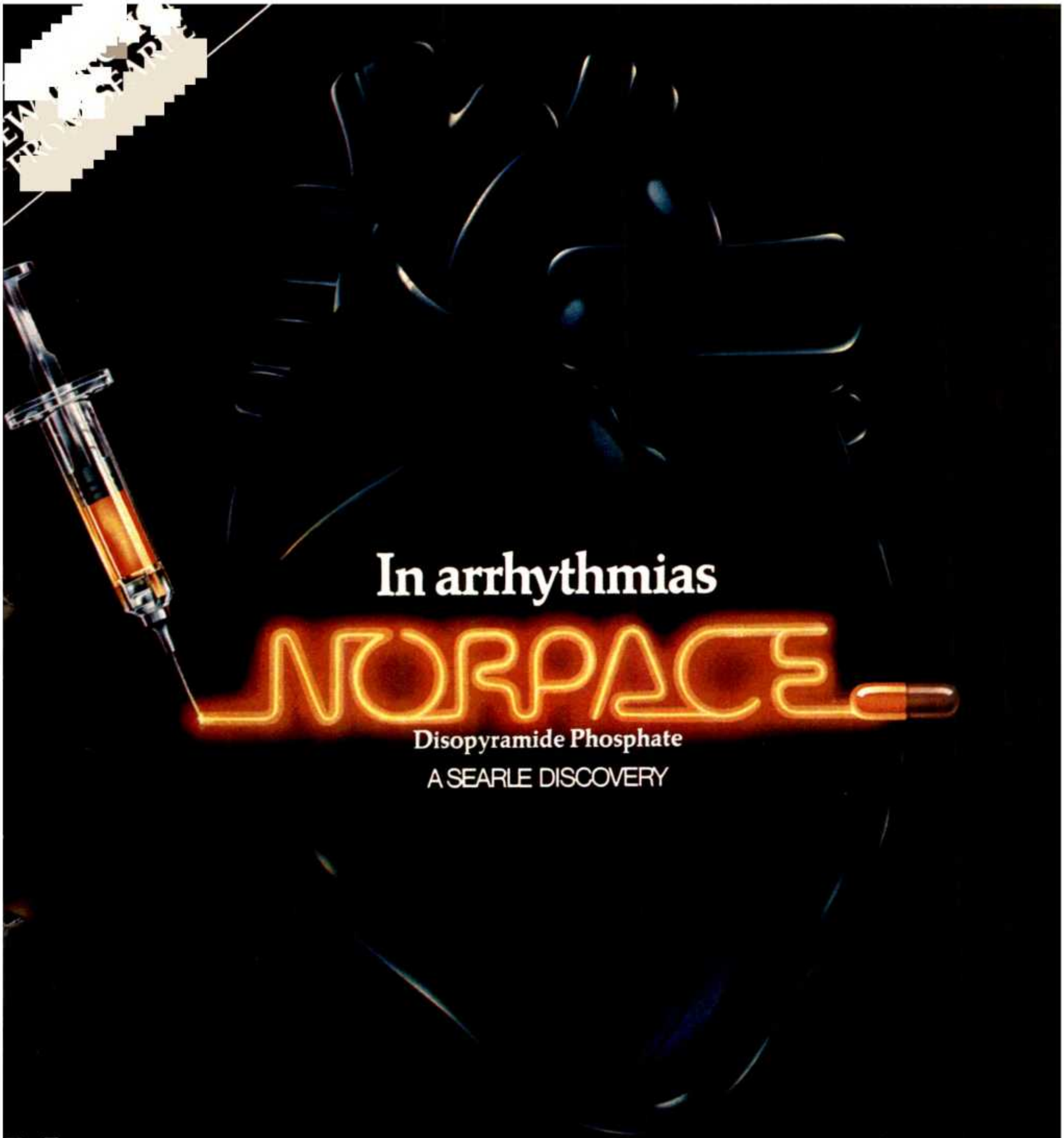

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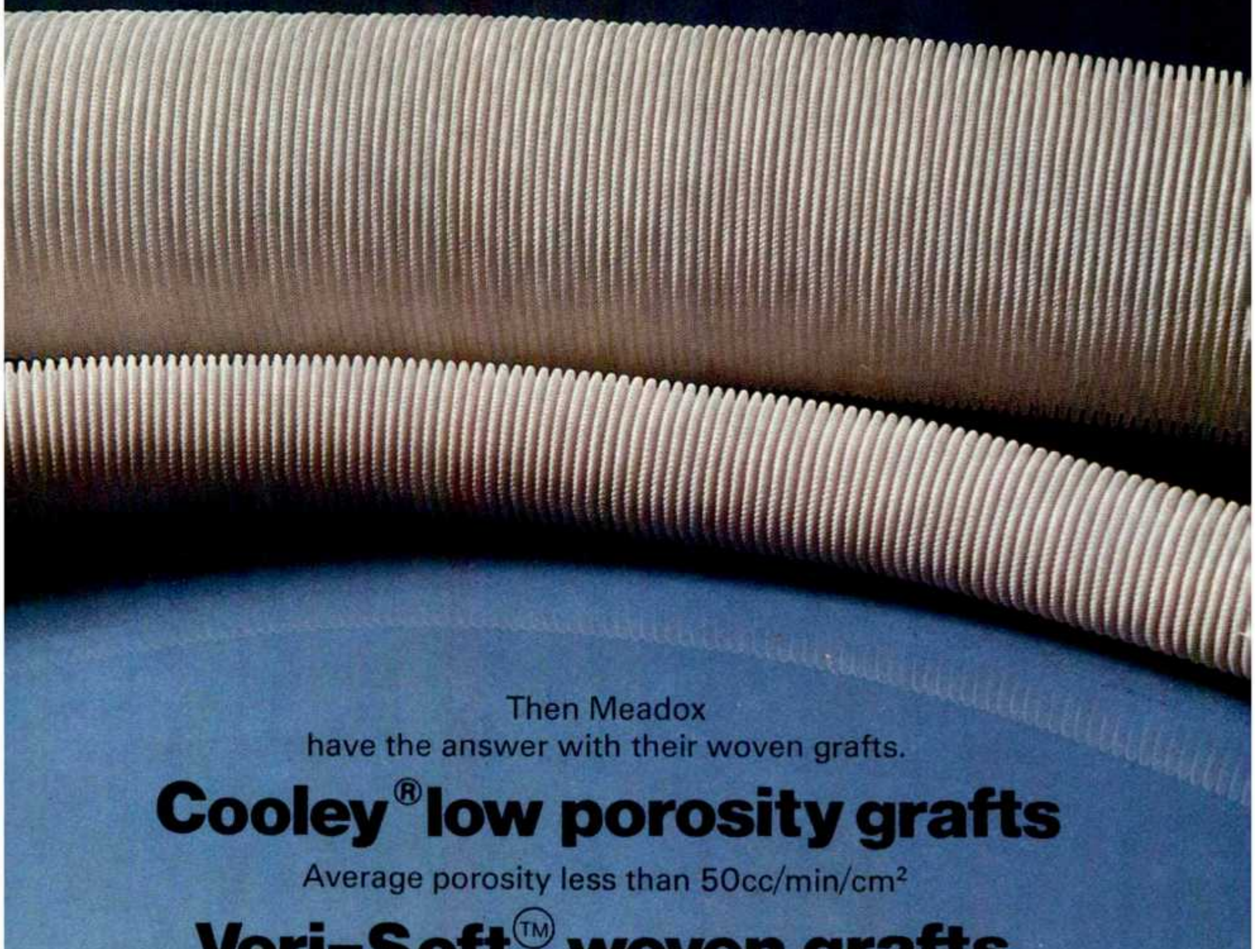

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Br Heart J 1980; **43:** 199–201

Large right atrial thrombosis

Rare complication during permanent transvenous endocardial pacing

G L NICOLOSI, P A CHARMET, D ZANUTTINI

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SUMMARY Right atrial thrombosis is a rare complication of permanent endocardial pacing. We report two cases with large right atrial thrombi which occurred during permanent endocardial electrical stimulation. Both patients were women, aged 83 and 89 years, who died suddenly, respectively, one month and 24 days after pacemaker implantation. At the time of death the two patients were in severe persistent refractory congestive heart failure despite appropriate medical treatment. At necropsy large mobile right atrial thrombi were found in both cases.

Venous thrombosis and embolisation are rare complications of permanent endocardial pacing.[1–14] Right atrial thrombosis has also occasionally been reported.[2]

London and co-workers[15] described two cases of right atrial thrombosis with subsequent haemodynamic impairment: the first in a 75-year-old man who died 48 hours after the insertion of the pacemaker, the second in a 69-year-old man who died two months after the implantation. In both cases, at necropsy, large right atrial thrombi surrounded the catheter electrode. In the first case the thrombus was approximately 80 per cent of the atrial cavity, in the second the transverse diameter of the thrombus range between 1·5 and 3·0 cm.

We report two cases of large right atrial thrombi found in a series of 53 necropsies performed in patients with permanent endocardial electrodes. Both cases were in congestive heart failure at the time of implantation and showed subsequent deterioration of an already impaired haemodynamic state.

Subjects

CASE 1

An 83-year-old woman with severe diabetes and chronic congestive heart failure underwent endocardial pacemaker implantation under local anaesthesia (lignocaine 2%, 20 ml) for complete heart block with syncopal attacks. An MIP 40 RT Vitatron unit connected to an MIP 147 electrode advanced via the right external jugular vein was implanted. During the procedure the patient experienced severe hypotension.

The patient subsequently recovered and was treated with insulin, digitalis, and diuretics. One month later she died suddenly, after mild fever during the last three days. At the time of death signs of chronic congestive heart failure were still present in spite of treatment. At necropsy a large spheroidal thrombus was found (4 cm diameter) eccentrically surrounding the catheter electrode in the right atrium. The thrombus was fastened to the atrial wall by two light strings of fibrous tissue (Fig. 1).

CASE 2

An 89-year-old woman underwent implantation of an MIP 40 RT Vitatron pacemaker connected to an MIP 147 electrode advanced via the left cephalic vein, because of atrial fibrillation, bifascicular block, and syncopal attacks. Chronic congestive heart failure was also present. The patient was treated medically and discharged on digitalis and diuretics. She was readmitted to the hospital 20 days later because of severe heart failure. On the fourth day after admission she died suddenly. At necropsy a scar was found consistent with an old anteroseptal myocardial infarction. Septal parietal thrombosis was present. A large thrombus (transverse diameter 3 cm) surrounded the catheter electrode in the right atrium; it was attached to the atrial wall by two large fibrous strands (Fig. 2).

Received for publication 6 August 1979

Discussion

Thromboembolic complications of permanent transvenous pacing rarely cause haemodynamic impairment or significant symptoms. London *et al.*[15] reported two cases with significant haemodynamic impairment caused by a large right atrial thrombus. Evidence of haemodynamic impairment, with signs of congestive heart failure, was present in both our cases at the time of implantation. Despite permanent transvenous endocardial pacing and medical treatment congestive heart failure did not improve as expected. In the first case persistence or even worsening of congestive heart failure was probably the result of mechanical obstruction in the right atrium. Sudden death might have been caused by acute obstruction of the tricuspid ring by the mobile thrombus. However, this could not be shown and major arrhythmias remain the other possibility. Thrombus formation might be related to the hypotensive episode during the implantation and possibly to dehydration caused by glycosuria.

In the second case the persistence of congestive heart failure and sudden death might also be related to the right atrial thrombus but major arrhythmias could not be excluded.

In patients undergoing permanent endocardial pacemaker implantation the persistence of refractory congestive heart failure in spite of treatment should call attention to the possibility of right atrial throbosis. This seems more likely to occur in elderly patients or after episodes of prolonged hypotension. As a diagnostic approach echocardiography or angiocardiography should be considered if signs of severe congestive heart failure persist or become worse despite a normally functioning endocardial pacemaker and proper medical support. In such cases sudden death can be the result, possibly from complete acute obstruction of the tricuspid valve by the mobile thrombus or because of major arrhythmias.

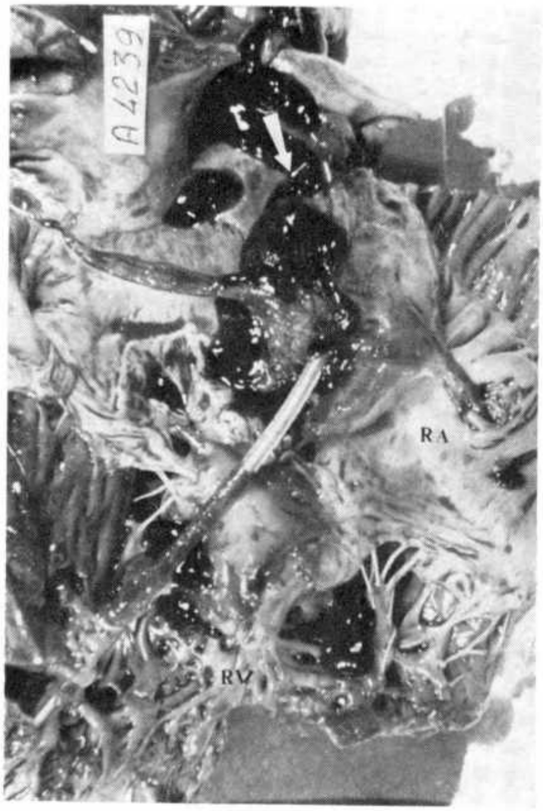

Fig. 1 *Thrombus surrounding the catheter electrode inside the right atrium* (arrow) *in case 1. RA, right atrium; RV, right ventricle.*

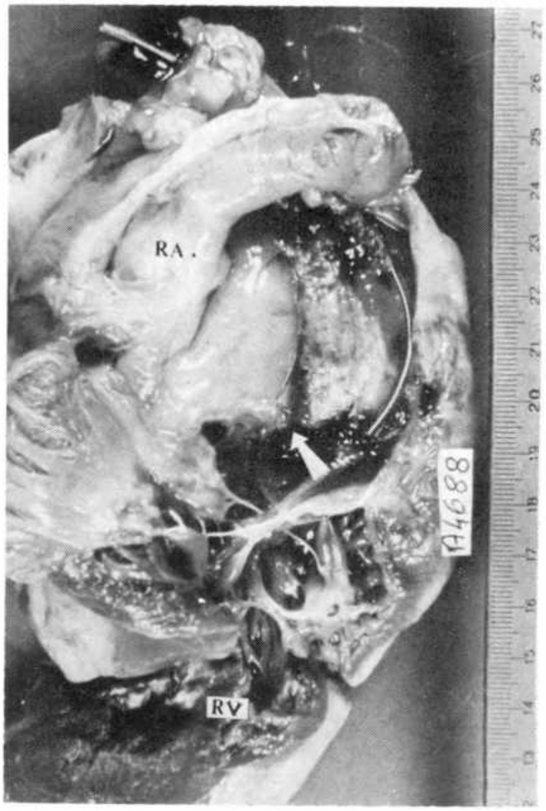

Fig. 2 *Thrombus surrounding the catheter electrode inside the right atrium, cut open* (arrow), *in case 2. RA, right atrium; RV, right ventricle.*

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Br Heart J 1980; **43**: 202–205

Clinical evaluation of Dinamap 845 automated blood pressure recorder

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SUMMARY The Dinamap 845 blood pressure recorder has been evaluated over a wide range of blood pressure by comparison with the Hawksley random zero sphygmomanometer in 32 subjects, six of whom had a cardiac arrhythmia. Group mean readings for systolic and phase 5 diastolic pressure were almost identical but Dinamap diastolic values were on average significantly lower (mean difference 3·4 mmHg) than phase 4 diastolic readings obtained with the Hawksley machine. Correlations between readings with the two instruments were high but the slopes and intercepts of the regression for systolic but not diastolic pressure were significantly different from unity and zero, respectively. The Dinamap is easy to use, portable, and capable of rejecting some motion artefact. Its major disadvantage is that the systolic blood pressure measurement is limited to a maximum of 210 mmHg, a point not made clear in the manufacturer's literature. Nevertheless, the Dinamap 845 is acceptable for blood pressure determinations in subjects who are normotensive or who have mild hypertension.

The mercury sphygmomanometer remains the standard device for measuring blood pressure in clinical practice and in clinical or epidemiological research. Modified versions such as the Hawksley random zero and London School of Hygiene sphygmomanometers have reduced the problem of observer bias in measurement, but inaccuracy resulting from differences between observers remains. To eliminate this many semiautomated blood pressure recording devices have been introduced. Their use has been criticised on the grounds that they are inaccurate, or that their accuracy has been poorly documented.[1] We have evaluated the Dinamap 845 automated blood pressure recorder, using the Hawksley random zero sphygmomanometer as the standard for comparison.

Methods

RECORDING DEVICES

The *Dinamap 845* (Fig. 1) is designed to monitor systolic, diastolic, and mean arterial pressure, and pulse rate. Manual determinations can be made using a switch on the front panel, or repeated fully automatic measurements can be obtained at chosen intervals between one and eight and a half minutes (since changed by the manufacturers to one to 16 minutes). The machine operates on an oscillometric principle measuring pressure fluctuation within a cuff,[2] and has no microphone or external transducer. Cuffs of three sizes are provided, enabling measurements to be made in obese patients or on the lower limbs. When the device is switched on the cuff is inflated automatically to 160 mmHg, and with subsequent automatic readings the cuff is pumped to a pressure approximately 34 mmHg higher than the previously determined systolic pressure. The cuff deflates in steps of 3 to 6 mmHg and the cuff pressure at each step is momentarily displayed. Errors from limited and intermittent motion artefact are detected and excluded using pulse amplitude averaging and error rejection programmes. When artefacts are detected the incremental cuff deflation cycle is halted until the artefact ceases, or until 60 seconds have passed when an alarm sounds and the cuff deflates completely. Recordings are interpolated between pressure steps during cuff deflation, and the step size does not apparently limit the accuracy of the measurements. Readings are displayed digitally on the front panel, and may also be recorded graphically using the Dinamap 950, which we did not test. The alarm mentioned above also sounds when mean arterial pressure is outside preselected high and low limits, and in the event of abnormal operating conditions, for example internal machine faults or measurements taking longer than three minutes.

Received for publication 15 August 1979

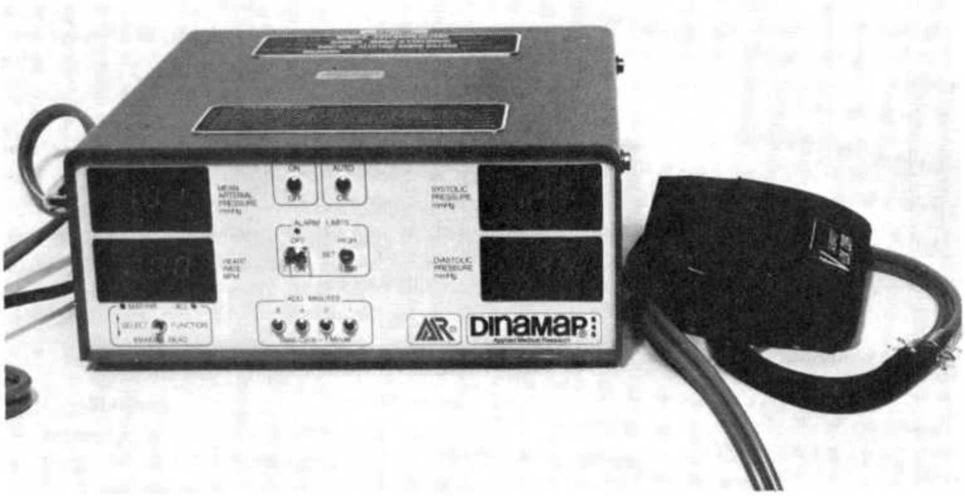

Fig. 1 *The Dinamap 845 blood pressure recorder.*

The Dinamap 845 weighs 7·5 kg, is portable, and is powered by mains electricity. A device using the same principles, but recording only mean arterial pressure and heart rate, has been tested against direct intra-arterial measurements.[3]

The *Hawksley random zero sphygmomanometer* is in essence a standard mercury sphygmomanometer with a zero muddle device to reduce observer bias.[4] The deflation rate was regulated to 2 to 3 mm/s. Measurements with this machine correlate well with intra-arterial pressures.[5]

Subjects

Twenty-seven patients and five healthy subjects were selected to provide a wide spread of blood pressure measurements. Nine of the patients had some abnormality of cardiac rhythm (atrial fibrillation in six, ventricular extrasystoles in three). One patient had an auscultatory gap, and two patients had persistence of Korotkoff sounds to 0 mmHg. In the latter patients phase 5 diastolic measurements were taken to be identical to phase 4 readings for the purpose of analysis. The range of arm girths was 18 to 34 cm, and a standard cuff size (23·5 × 13·5 cm) was used in all patients with both machines.

PROCEDURE

After five minutes recumbent four pairs of simultaneous measurements were taken, with the Dinamap on one arm, the Hawksley on the other. The machines were changed to the other arm after each measurement. The Dinamap was used on the right arm first in alternate subjects. Pressure measurements were read to the nearest 1 mmHg with both devices. Systolic, diastolic phase 4, and diastolic phase 5 pressures were recorded with the Hawksley, and mean arterial pressure was calculated as diastolic phase 5 plus one-third pulse pressure. Systolic, diastolic, and mean arterial pressures were read from the Dinamap. The observers did not communicate with each other until all recordings in one subject were complete. The mean of the four readings in each subject was calculated for each machine, so that the comparison of the machines was not biased by variations in blood pressure with time or between the two arms. The mean results for each recorder were compared by Student's t test for paired observations, and product-moment correlation coefficients were calculated. The calculated regression lines were examined to determine whether their slopes deviated significantly from unity, and their intercepts from zero.

Results

FAILURE TO OBTAIN RECORDINGS

Satisfactory measurements could not be obtained in three subjects, with failure of the Dinamap 845 in two, and failure of the Hawksley (or, more precisely, of the auscultatory method) in one. The Dinamap was consistently incapable of measuring the blood pressure in one patient with atrial fibrillation, though it recorded satisfactorily in the other five patients with this arrhythmia. It also failed to record in one patient with a systolic blood pressure of 260 mmHg, and we discovered subsequently that the device was incapable of measuring pressures

Table *Group mean data (±SD) showing* (a) *arterial pressure values, and* (b) *within-subject standard deviation in blood pressure readings obtained when using the Dinamap 845 and the Hawksley random zero sphygmomanometer*

		Blood pressure (mmHg)			*Within-subject standard deviation (mmHg)*		
		Dinamap	*Hawksley*	*P*	*Dinamap*	*Hawksley*	*P*
Systolic		152·8 ±30·4	152·7 ±34·2	NS	6·29 ±3·41	5·62 ±3·26	NS
Diastolic	Phase 4	86·6 ±18·3	90·0 ±18·3	<0·01	4·06 ±3·23	5·06 ±3·23	NS
	Phase 5		86·5 ±19·1	NS		4·80 ±2·83	NS
Mean pressure		103·9 ±19·3	108·6* ±23·0	<0·01			

* Derived from phase 5 diastolic blood pressure + ⅓ pulse pressure. P, Significance between Dinamap and Hawksley determinations.

higher than 210 mmHg. In both of these patients the alarm sounded repeatedly when measurements were attempted. The Hawksley device failed to provide readings in one patient with ventricular bigeminy because the observer was uncertain of the true systolic pressure.

ACCURACY OF DINAMAP 845

The data for the remaining 29 subjects are shown in the Table. The Dinamap systolic and diastolic pressures were virtually identical to the Hawksley systolic and phase 5 diastolic pressures, respectively. Dinamap diastolic pressures were on average 3·4 mmHg lower than Hawksley phase 4 readings (P<0·001). The mean arterial pressure read from the Dinamap was 4·7 mmHg lower than mean arterial pressure calculated from the Hawksley measurements (P<0·002). Correlations between readings with the two instruments were high (Fig. 2); (a) Dinamap systolic v. Hawksley systolic, r=0·98; (b) Dinamap diastolic v. Hawksley phase 5, r=0·96; (c) Dinamap diastolic v. Hawksley phase 4, r=0·96; (d) Dinamap mean arterial pressure v. Hawksley mean arterial pressure, r=0·95. The slopes and intercepts were (a) 0·88, 19 mmHg; (b) 0·91, 6 mmHg; (c) 0·91, 8 mmHg; (d) 0·79, 18 mmHg, respectively. Significant differences from unit slope and zero intercept (P<0·01) were noted only for systolic (a) and mean (d) blood pressure. In an individual, readings obtained by the two instruments were equally consistent.

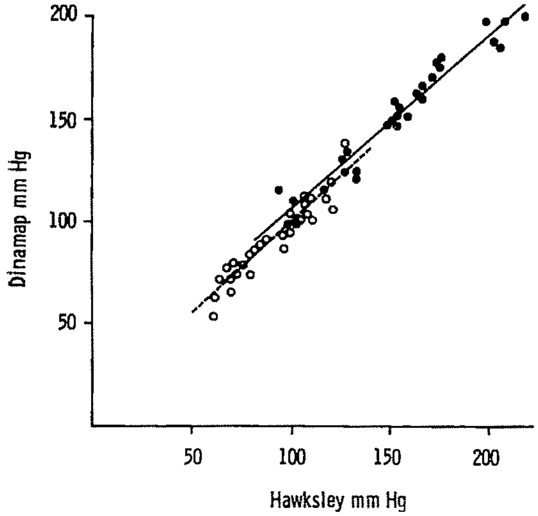

Fig. 2 *Correlation between blood pressure values obtained using the Hawksley sphygmomanometer and the Dinamap 845. Closed circles, systolic r=0·98, slope 0·88, intercept 19 mmHg; open circles, diastolic (phase 5) r=0·96, slope 0·91, intercept 6 mmHg.*

PERFORMANCE OF DINAMAP 845

Measurements with the Dinamap were usually complete in about 40 seconds, on average slightly quicker than the Hawksley readings. Placement of the cuff did not appear to be critical. The alarm system seemed to function well. The performance of the machine we tested deviated in two important respects from the specifications given in the manufacturer's literature, and described in the Methods section. Most surprising was the failure of the device to measure pressures above 210 mmHg. This is not mentioned in the literature, though the manufacturers were in fact aware of it. The cuff deflation steps in the instrument were 8 to 10 mmHg, and not the 3 to 6 mmHg quoted.

Discussion

The Dinamap 845 faithfully reflected systolic and diastolic blood pressure readings within the range 50 to 200 mmHg. Though the regression line for systolic blood pressure deviated from a unit slope with zero intercept, the difference did not seem clinically important in the range of blood pressure tested (Fig. 2). The close agreement with phase 5 as opposed to phase 4 diastolic values is no disadvantage since this is the criterion used in most epidemiological studies.[6, 7] The mean arterial pressure did not correspond closely but it is known that the derived values obtained by the mercury manometer are an approximation[8]. Mean arterial pressure obtained with an earlier Dinamap model corresponded closely with intra-arterial pressures.[3]

In general, blood pressure measurements were not hampered by arrhythmias, a silent interval, or persistence of Korotkoff sounds to zero. There were no grossly erroneous readings and the alarm system functioned well.

The machine is light and therefore easily portable, quick, and simple to use and required no ultrasonic gel. As cuff position is not critical it should be accurate in the hands of an inexperienced observer, and we made no effort to effect exact cuff placement.

The major disadvantage of the device is that systolic blood pressure measurement is limited to a maximum of 210 mmHg. This limits the machine's use to subjects who do not have severe hypertension. Furthermore, it is necessary to exclude the first reading in subjects with a systolic blood pressure above 155 mmHg. This is not a significant defect when repeated blood pressure measurements are required but is a disadvantage with single determinations. In such a situation, however, a potential error may be accurately predicted from the display of cuff pressure during each deflation step.

The method used to eliminate errors arising from motion artefact leads to a delay in blood pressure determination. This is likely to be a problem when there is continuous movement artefact with brief pauses that enable the cuff to be deflated slightly. In such an event it is possible for the cuff to be kept above the subject's systolic pressure for up to 3 minutes. Decreasing the constant pressure alarm criterion from 60 seconds would make this unusual problem less likely to cause discomfort.

The Dinamap 845 has a useful place for repeated blood pressure determinations in subjects with normal blood pressure or with mild hypertension. It may prove useful in an intensive care unit though the machine has yet to be tested at blood pressure values below 90/50 mmHg. The consistency between different machines and of an individual instrument over a period of time also remains to be demonstrated. Finally, deficiencies in the manufacturer's literature need to be rectified.

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Br Heart J 1980; **43**: 206–210

Salbutamol in treatment of heart failure

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SUMMARY The haemodynamic effects of oral and intravenous salbutamol were investigated in 22 patients with chronic heart failure. Intravenous salbutamol (13 μg/min) increased cardiac index by 53 per cent from 1·5±0·13 l/min per m^2 to 2·3±0·23 l/min per m^2 and decreased systemic vascular resistance by 28 per cent from 29·4±3·9 units to 21·2±2·5 units. Heart rate rose by 10 per cent from 101±3·5 beats per minute to 111±3·2 beats per minute and pulmonary artery end-diastolic pressure fell by 13 per cent from 26·3±1·8 mmHg to 22·8±2·1 mmHg. Similar results were obtained after oral salbutamol (8 mg). Cardiac index rose by 40 per cent and systemic vascular resistance fell by 30 per cent. There was a small rise in heart rate and a variable and not significant change in pulmonary artery end-diastolic pressure. Experiments on isolated rabbit papillary muscle showed that salbutamol, at the concentration which exists in patients, had no detectable positive inotropic effect. It is probable that the increase in cardiac output in patients is primarily the result of reduced afterload caused by vasodilatation. Salbutamol is a useful drug in the treatment of chronic heart failure.

Vasodilator drugs are widely advocated in the treatment of both acute and chronic heart failure.[1–3] Salbutamol is a relatively specific beta-2 adrenergic agonist which relaxes smooth muscle and reduces systemic vascular resistance.[4] The haemodynamic effects of intravenous salbutamol have been studied in normal persons,[5] in patients with respiratory disease,[6] in patients after acute myocardial infarction,[7] in patients with mitral valve disease,[8] and in patients after cardiac surgery.[9–11]

More recently Sharma and Goodwin[12] reported the effects of intravenous salbutamol in patients with congestive cardiomyopathy and concluded not only that the drug was beneficial but that its primary action was as a positive inotropic agent. The purpose of the present study was to investigate the haemodynamic effects of both oral and intravenous salbutamol in patients with chronic heart failure. In an attempt to establish whether the effects of salbutamol were attributable to vasodilatation or increased cardiac contractility, experiments were undertaken on isolated right ventricular papillary muscles of rabbits.

Patients

Salbutamol was administered by either the oral or the intravenous route. Group A consisted of 11 patients given salbutamol 8 mg orally. There were nine men and two women, aged 31 to 67 years, mean 52 years. Heart failure was the result of coronary artery disease in nine and cardiomyopathy in two. All patients were in sinus rhythm apart from one patient who had a permanent pacemaker implanted for complete heart block.

Group B consisted of 11 patients given intravenous salbutamol in a dose of 13 μg/min. There were 10 men and one woman, aged 49 to 78 years, mean 65 years. Heart failure was the result of coronary artery disease in 10 patients and congestive cardiomyopathy in one. All but one patient, who was in atrial fibrillation, were in sinus rhythm.

All patients in both groups had severe heart failure which had not responded satisfactorily to large doses of diuretics. All except four patients were on digoxin. Six of the patients in Group A were able to walk short distances in the ward. The remaining seven patients in Group A and all patients in Group B were confined to bed by the severity of their heart failure.

Methods

Cardiac output was measured by the thermodilution technique using a Swan-Ganz catheter and a cardiac output computer (Edwards Laboratories, Model 9510—A; Cardiovascular Instruments,

Received for publication 30 July 1979

Model 600). For each measurement the average of three estimations was calculated. The catheter was inserted percutaneously into a subclavian vein and advanced to the pulmonary artery. Measurements were made of the right atrial pressure, pulmonary artery wedge pressure, and pulmonary artery pressure. The wedge pressure correlated closely with the pulmonary artery end-diastolic pressure in all patients. In subsequent recordings the pulmonary artery end-diastolic pressure was used to assess changes in left ventricular filling pressure in most patients in order to avoid frequent manipulation of the catheter. The zero reference point was the sternal angle. Blood pressure was measured with a sphygmomanometer and the heart rate was obtained from the electrocardiogram. Mean blood pressure was calculated as the diastolic pressure plus a third of the pulse pressure. Systemic vascular resistance was calculated as the difference between the mean blood pressure and right atrial mean pressure divided by the cardiac output. Stroke volume index was calculated from the cardiac index and heart rate.

In group A patients, measurements were made at rest and after administration of 8 mg oral salbutamol, at half-hourly intervals for two hours and subsequently at one- or two-hourly intervals for a maximum of seven hours. In six patients two sets of control measurements were made one hour apart. Only small and insignificant changes were observed.

In group B measurements were made under control conditions and 40 minutes after the start of an infusion of salbutamol at a dose of 13 μg/min.

Experiments were undertaken on isolated right ventricular papillary muscles of rabbits (2 to 4 kg). The experimental preparation has been previously described.[13] Temperature was 37°C and the stimulation rate 60 beats per minute. The muscles were stretched until developed tension was maximal. Developed tension and the first differential of developed tension (dT/dt) were recorded.

Results

GROUP A: ORAL SALBUTAMOL

The changes in cardiac index over the period of the study are shown in Fig. 1. There was a rise in all patients with a peak at an average time of 90 minutes. Cardiac index subsequently fell slowly but did not reach control levels within seven hours.

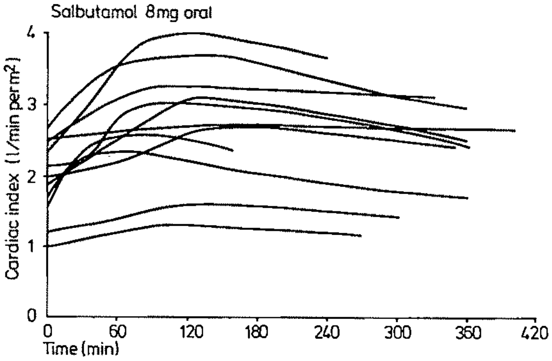

Fig. 1 *Group A. The changes in cardiac index after oral salbutamol (8 mg).*

The changes in cardiac index, heart rate, pulmonary artery end-diastolic pressure, systemic arterial mean pressure, systemic vascular resistance, and stroke volume index at the time of maximum cardiac index are shown in Fig. 2. Cardiac index rose from 2·0 ±0·16 l/min per m^2 to 2·8 ±0·27 l/min per m^2 after salbutamol (40%, $p<0\cdot001$). Heart rate increased from 83 ±3 to 89 ±4 beats per minute (7%, $p<0\cdot05$). Pulmonary artery end-diastolic pressure fell in six patients, but for the whole group there was no significant change. There was no significant change in mean blood pressure which was 86 ±1·8 mmHg before and 82 ±2·7 mmHg after salbutamol. Calculated systemic vascular resistance fell from 24·9 ±2·8 units before to 17·4 ± 2·2 units after salbutamol (30%, $p<0\cdot001$). Stroke volume index increased from 25·6 ±2·6 to 31·8 ±3·0 ml/m^2 (28%, $p<0\cdot001$).

One patient in group A had an episode of angina associated with tachycardia two hours after salbutamol. This patient was treated with sublingual glyceryl trinitrate and the study was discontinued. No other side effects were observed.

GROUP B: INTRAVENOUS SALBUTAMOL

The results are shown in Fig. 3. Cardiac index rose in all patients from 1·5 ±0·13 l/min per m^2 before salbutamol to 2·3 ±0·23 l/min per m^2 (53%, $p<0\cdot001$) 40 minutes after the start of the salbutamol infusion. There was a small but significant increase in heart rate from 101 ±3·5 to 111 ±3·2 beats per minute (10%, $p<0\cdot01$). Pulmonary artery end-diastolic pressure fell in seven patients and the fall was significant for the group as a whole, from 26·3 ±1·8 to 22 ±2·1 mmHg (13%, $p<0\cdot01$). The mean blood pressure rose slightly from 80·5 ± 5·5 mmHg before to 84·6 ±5·3 mmHg after salbutamol (5%, $p<0\cdot05$). There was a 28 per cent fall in calculated systemic vascular resistance from 29·4 ± 3·9 to 21·2 ±2·5 units ($p<0\cdot001$). Stroke volume index increased from 15·0 ±1·2 to 20·6 ±2·1 ml/m^2 (37%, $p<0\cdot001$).

In one patient the infusion of salbutamol had to be discontinued because of the appearance of multiple ventricular ectopic beats. There were no other observed side effects in the patients in group B.

Of the patients in group A, two died from deterioration of heart failure within four weeks of the initial study, and one died at the time of coronary artery bypass operation six weeks after the study. Five patients treated with oral salbutamol (4 mg q.d.s) reported an improvement in their symptoms of breathlessness and three patients were symptomatically unchanged. Of the patients in group B, seven died from deterioration of heart failure within four weeks of the initial study. Two of the remaining patients reported a symptomatic improvement on oral treatment.

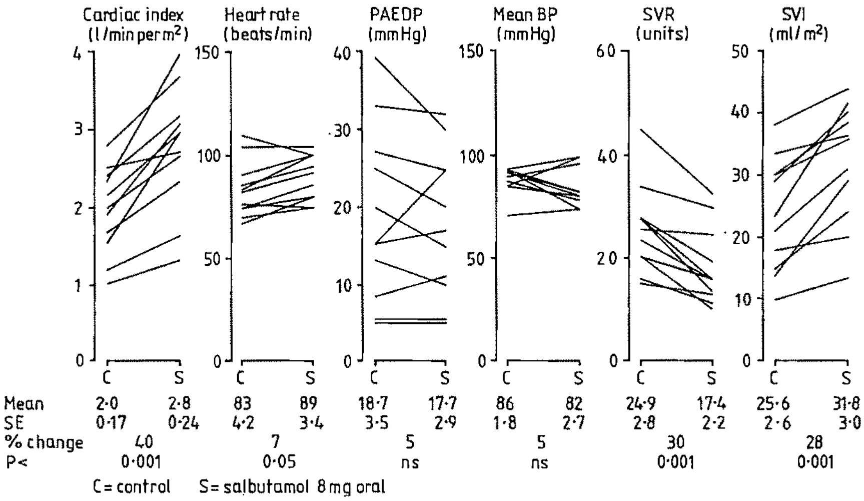

Fig. 2 *Group A. Haemodynamic changes after oral salbutamol (8 mg). The changes in cardiac index, heart rate, pulmonary artery end-diastolic pressure (PAEDP), mean blood pressure (BP), systemic vascular resistance (SVR), and stroke volume index (SVI) are recorded in each case at the time of maximum cardiac index.*

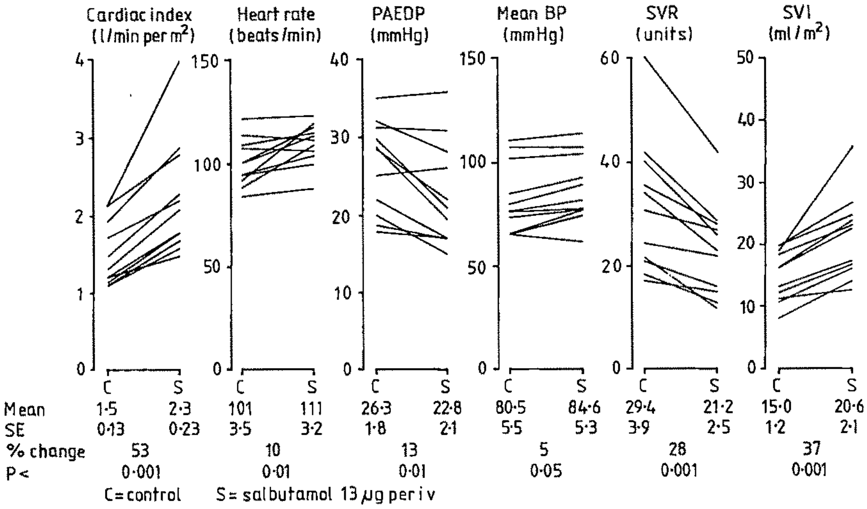

Fig. 3 *Group B. Haemodynamic changes during intravenous salbutamol infusion (13 µg/min). The changes in cardiac index, heart rate, pulmonary artery end-diastolic pressure (PAEDP), mean blood pressure (BP), systemic vascular resistance (SVR), and stroke volume index (SVI) are recorded in each case 40 minutes after the salbutamol infusion was started.*

IN VITRO STUDIES

The changes in developed tension with increasing concentrations of salbutamol in a single experiment are shown in Fig. 4. There is no detectable change with a concentration of 0·01 mg/l. A dose-response curve is shown in Fig. 5 in which a significant increase in developed tension occurs at concentrations of 0·1 mg/l and above. Similar changes occurred in the positive and negative differential of developed tension.

Discussion

Oral and intravenous salbutamol have similar haemodynamic effects in patients with chronic heart failure. Salbutamol increases cardiac index and reduces systemic vascular resistance with a small increase in heart rate and a variable or small fall in pulmonary artery end-diastolic pressure. The percentage rise in mean cardiac index (53%) and the fall in systemic vascular resistance (30%) in patients given intravenous salbutamol are similar to those found by other workers in patients after cardiac surgery,[11] with congestive cardiomyopathy,[12] and with mitral valve disease.[8] We did not find the same rise in heart rate as did Poole-Wilson *et al.*[11] and Gibson and Coltart,[8] but the smaller change in our patients is similar to that recorded by Sharma and Goodwin[12] in patients with cardiomyopathy and some degree of cardiac failure. It appears that in patients with heart failure the effect of salbutamol on heart rate is small.

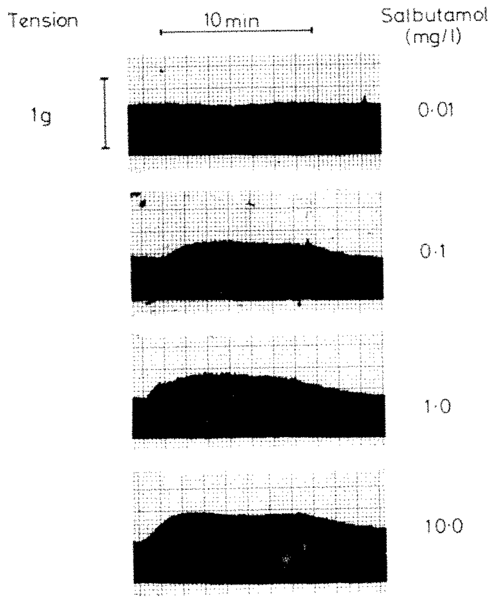

Fig. 4 *Changes in developed tension in isolated right ventricular papillary muscle of a rabbit with increasing concentrations of salbutamol.*

Several differences were apparent under control conditions between the groups of patients given oral and intravenous salbutamol. The group given intravenous salbutamol had more severe heart failure, were more limited by symptoms, had a lower cardiac index ($p < 0{\cdot}05$) and stroke volume index ($p < 0{\cdot}001$), and had a higher heart rate ($p < 0{\cdot}01$). Both groups of patients responded to salbutamol in a similar manner, in that cardiac index increased and systemic vascular resistance fell (Fig. 2 and 3) but in the group given intravenous salbutamol there was a rise in blood pressure and a fall in pulmonary end-diastolic pressure, which were not seen in the group given oral salbutamol. These differences might be attributable to the different routes of administration of the drug but are more probably a reflection of the more severe heart failure in the group given intravenous salbutamol. The pulmonary artery end-diastolic pressure in the group given oral salbutamol fell in the five patients with the highest initial pressures; the failure of the group as a whole to show a significant fall is partly the result of the inclusion of patients whose control pulmonary artery end-diastolic pressures were low as a result of treatment with powerful diuretics. In these patients the pulmonary artery end-diastolic pressure presumably increases on the mildest exertion since breathlessness was the predominant symptom. Even in the group given intravenous salbutamol the fall in

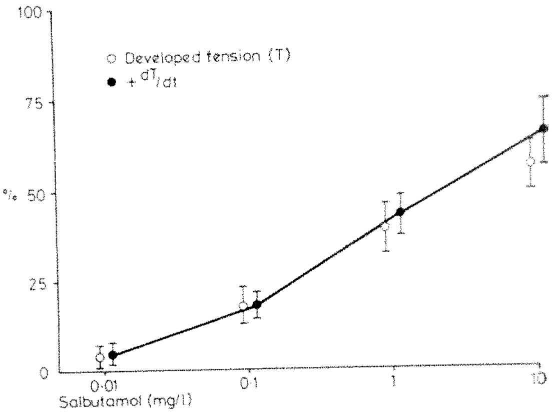

Fig. 5 *Dose-response curve for changes in developed tension (T) and dT/dt in isolated rabbit right ventricular papillary muscle ($n = 5$) with increasing concentrations of salbutamol.*

pulmonary artery end-diastolic pressure, though statistically significant, was small (3·5 mmHg).

The haemodyanamic effects of salbutamol could be the consequence of vasodilatation or the result of a positive inotropic effect. The former is more probable since salbutamol is known to be a beta-2 agonist[4] with beta-1 activity only at high concentrations. The problem cannot be resolved in vivo because of the difficulties in distinguishing between an increase in cardiac output resulting from a fall in systemic vascular resistance and an increase in cardiac output resulting from increased contractility with reflex vasodilatation. The in vitro experiments reported here show no significant positive inotropic effect at a concentration of 0·01 mg/l. Though plasma salbutamol concentration was not measured in this study, previous work (D A Richards, 1978, personal communication) has shown a linear relation between infusion rate maintained for one hour and mean plasma salbutamol concentration. Infusion rates of 50, 40, and 30 μg/min produced plasma concentrations of 0·036, 0·027, and 0·022 mg/l, respectively. The estimated plasma concentration with an infusion rate of 13 μg/min would be 0·009 mg/l, a concentration which produced no positive inotropic effect in isolated rabbit papillary muscle. Though considerable caution is required in applying animal results obtained in vitro to studies in man, equally our findings do not lend support to the suggestion[12] that the effects of salbutamol in the doses used in this study are primarily a result of a positive inotropic action. The increase in cardiac output is probably consequent upon the reduction of systemic vascular resistance.

Our results show clearly that oral and intravenous salbutamol increase cardiac output. The fall in pulmonary artery end-diastolic pressure was small and a drug with a greater venodilator effect may be indicated in patients with heart failure and a high pulmonary artery end-diastolic pressure at rest. Though we have used salbutamol orally (4 mg q.d.s.) for periods greater than two months in 10 patients with severe chronic heart failure, we have no objective evidence of improvement. Nevertheless, our clinical impression is that in these patients symptomatic benefit is appreciable and side effects rare. A beneficial effect is by no means invariable and we have found no simple method of selecting those who will improve. Salbutamol can also be useful in the treatment of patients confined to bed in hospital with heart failure and oedema unresponsive to large doses of diuretics and digoxin. Intravenous salbutamol was given to such patients for periods of three to 20 days. This treatment enabled patients who previously were languishing in hospital beds to return home.

We wish to thank Glaxo Group Research Ltd. and Allen & Hanbury Ltd. for their assistance.

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Br Heart J 1980; **43:** 211–219

Second report of a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England on combined cardiac centres for investigation and treatment with a note on the requirements of cardiology in hospitals outside such a centre

> *'In issuing this report of the Joint Working Party, and in welcoming its general recommendations, the two Colleges emphasise that these plans, if they are to be fulfilled, will require time for further discussion on such important aspects as access to training for those in medicine and surgery who require experience in cardiac work, and the implications for specialties such as radiology and anaesthesia. The two Colleges also regard it as essential that adequate additional funding is provided in such a way as to impose no detriment on the existing services.'*

SUMMARY (1) This, the second report of a Joint Cardiology Committee of the Royal College of Physicians of London, and the Royal College of Surgeons of England, on combined cardiac centres for investigation and treatment updates the original report of 1967. (2) The following recommendations should be considered as a design for a modern cardiac centre and are based on current demands and developing trends. (3) The past decade has seen the establishment of a number of new investigatory techniques such as coronary arteriography, left ventriculography, echocardiography, the use of radionuclides, and the development of sophisticated electrophysiological techniques. In addition, there has been a change of emphasis in cardiac surgery. (4) Coronary artery bypass grafting has become established internationally as a low-risk procedure for relieving cardiac pain. In certain cases there may also be a benefit in terms of life expectancy. (5) The demand for surgical treatment of valve disease and congenital heart disease continues. (6) Recommendations are made regarding: (a) workload, (b) siting, (c) staffing, and (d) size of a modern cardiac centre: (6a) Centres should be capable of undertaking a minimum of 200 open-heart operations a year. (b) They should be sited in relation to a general or university teaching hospital. (c) Staffing should be calculated on the basis of providing a 24-hour service as well as taking into account the needs for teaching and research. To achieve maximum efficiency and economy each centre will require three consultant cardiac surgeons and supporting staff. It is estimated that they and their teams could achieve approximately 600 open-heart operations per year. (d) The size of a centre will ultimately depend on the size of the population served. Data available from South Australia and Scotland suggest that 600 open-heart operations a year might be expected from a community of approximately two million. (7) Cardiac centres must be a regional or, preferably supraregional, responsibility. They should receive directly earmarked funds allocated on a national basis. Competition for funds at district level must be avoided. (8) It is envisaged there will be a limited number of special paediatric centres. These will be associated with a major cardiac centre and wherever possible with a paediatric department of a university hospital. At these centres there will be special expertise for neonatal and infant cardiac surgery. Much of the routine paediatric work, especially for older children, will be done in the ordinary cardiac centres and in the paediatric departments of general and university teaching hospitals. (9) Requirements for a cardiac department in regional hospitals and hospitals not directly associated with a major cardiac centre are outlined. (10) In view of the rapid developments and changes in cardiovascular medicine and surgery, this report should be reviewed in not more than five years by a joint committee of the Royal College of Physicians and Royal College of Surgeons, and thereafter as recommended.

In 1967 a Joint Cardiology Committee of the Royal College of Physicians of London and the Royal College of Surgeons of England was set up to study and report on the need for special centres for diagnosis, treatment, and research. The report published in 1968[1] laid down the principles and the requirements of a combined medical and surgical cardiac centre (subsequently referred to as cardiac centre) but financial constraints and changes in priorities in the medical field have limited the implementation of the original report. As there have been many advances and changes in treatment during the past decade it was decided to convene a second committee of the two colleges to re-examine the problem.

In the past 10 years established investigations such as coronary arteriography and left ventriculography have been improved and refined while new techniques such as echocardiography, the use of radionuclides, and sophisticated electrophysiological procedures for the study of arrhythmias have all become established and are now a routine part of diagnostic cardiology. During the same period there has been an increase in demand for and changes of emphasis in cardiac surgery. This is particularly evident in coronary artery disease where bypass grafting has been internationally accepted as a low-risk procedure for relieving cardiac pain. There may also be benefits in terms of life expectancy in patients with some forms of coronary artery disease, particularly that involving the left main coronary artery.[2] The multicentre European trial that was organised in 1972 to study the effect of surgical treatment on prognosis in patients with stable angina has shown that there is a statistically significant advantage in surgery compared with medical treatment in patients with important disease of the three principal coronary arteries: left anterior descending, circumflex, and right coronary arteries.[3] Ten years ago this type of surgery was not available. While full benefits and the limitations of the operation have still to be defined, the results so far indicate that it is likely to be performed for certain types of coronary heart disease with increasing frequency in the foreseeable future. There has also been a change in the surgery for valvar disease for, though the incidence of chronic rheumatic heart disease has fallen and the benefits of conserving reparable valve tissue are generally accepted, the lower operative mortality and reduction of late complications resulting from improved mechanical and tissue valves have led to the wide use of valve replacement in this and, indeed, in valvar lesions of all types. It is unlikely that there will be an appreciable reduction in the number of patients requiring this type of surgery for at least the next five years.

In spite of the falling birth rate there has been no reduction in the number of patients requiring surgery for congenital heart disease, which reflects the increasing expertise and scope of operations available for this age group.

Thus, the character of cardiac surgical treatment has changed, the demand is increasing and, owing to the frequency of coronary artery disease, this trend is likely to continue for at least the next decade.

The report that follows, as in the first report, sets out recommendations in broad outline, concentrating on principles rather than details. It assumes that the increase in cardiovascular work over the past 10 years is likely to continue. Accordingly, further expansion of existing facilities must be envisaged and it is essential that they are adequately financed. The design of centres must be sufficiently flexible to allow for the changing demands and integration of new diagnostic and therapeutic techniques.

The committee recognises that cardiac centres will vary in size and situation according to local circumstances. The recommendations for staffing take into account the exacting nature of the work, the need for full service throughout the 24 hours, as well as the importance of teaching and research.

Objectives and siting of a cardiac centre

The centre should provide for the investigation of patients whose cardiac disease may require surgical treatment and also for those needing evaluation by modern diagnostic techniques who will be treated medically. The cardiac centre should be responsible for cardiac pacing services for a wide area. In the cardiovascular field diagnosis and treatment are so intimately linked that the care of patients must be the joint responsibility of physicians and surgeons including those involved in specialised investigation such as invasive radiological techniques and the use of radionuclides. Optimal clinical results and research can be achieved only when all personnel concerned function as an integrated team.

The cardiac centre should be sited in association with a general hospital because of the many supporting facilities needed and because of the undisputed value of remaining in close contact with other medical and surgical disciplines. Ideally, the cardiac centre should lie within the orbit of a university medical school where facilities for research are already concentrated. The committee recognises the excellent work done by special hospitals and institutes of cardiology which are not sited in association with a general hospital but it emphasises that such institutes and hospitals have to make special arrangements to enjoy the advantages of a general hospital and university medical school environment. The main disadvantages of isolation are lack of basic science and academic influence, support facilities, and the absence of close liaison with other important disciplines in medicine, surgery, and paediatrics. Furthermore, the training of junior staff may suffer if carried out solely in a specialised unit. Thus, planning for new cardiac centres should take account of these factors. Much cardiovascular work of a less specialised nature is carried out and should continue in hospitals that do not have specialised centres, as outlined above.

Size of unit and workload

The optimum size of a cardiac centre has not yet been determined. There are many factors, local, national, and international, that must be taken into account. In making recommendations, the committee has considered data which are summarised below.

The needs of a population have been assessed in South Australia and Scotland. The most comprehensive figures available come from South Australia where, in 1975, approximately 300 open-heart operations were performed per 1 000 000; 55 per cent were for coronary artery disease, 30 per cent for acquired valvar disease, and 15 per cent for congenital heart disease. Coronary artery surgery has increased dramatically but the amount is still less than anticipated by the WHO Committee.[4] Currently in the United Kingdom the amount of coronary artery surgery is far below this level, being only 30 per 1 000 000 population or one-sixth of the rate in South Australia.[5]

Similar figures are available from the report of the Scottish Home and Health Department on cardiac surgery in Scotland, which stated that for Edinburgh with a population of 1·2 million, 268 cardiac operations were undertaken in the year 1975.[6] In view of the increasing waiting list 352 operations annually were predicted for the future, a figure which is remarkably close to that from South Australia. Applying the Edinburgh experience to the whole of Scotland, which has a population of 5·2 million, the Scottish Committee anticipated that the current demand would be for 1525 operations annually. The World Health Organisation Report on the 'Long term effects of coronary bypass surgery',[4] states that the needs for surgery will be between 230 and 1000 operations per year per million population depending upon the attitude of the physicians who refer patients.

On the basis of figures for open-heart operations in South Australia in the WHO and in the Scottish reports it appears that England and Wales could generate between 15 000 and 20 000 open-heart operations per annum. However, the Cardiac Surgical Register for 1976[7] recorded between 7000 and 8000 operations for the whole of the UK: thus considerable expansion must be anticipated.

The potential of any cardiac centre is usually limited by its surgical output, and the amount of work the physicians and surgeons can do efficiently determines the population which can be served. The size and facilities of a cardiac centre must be adequate to allow all physicians and surgeons to employ their clinical, teaching, and research abilities to the full.

A centre must have at least three consultant cardiac surgeons (see p. 214). Two consultant surgeons are insufficient for, with periods of leave for study and lecturing, vacation purposes, or sickness, approximately 20 per cent of the year's work would be the responsibility of one surgeon. This situation would not provide sufficient cover for routine and emergency operations and would place an excessive burden on the surgeon concerned and on his team. In addition, consultants may wish, after many years of intensive operating, to reduce their load, particularly of highly complex and demanding surgery. The number of operations performed annually would naturally depend upon many factors and over-rigid recommendations should be avoided in order to maintain maximum flexibility. Nevertheless, the committee believes that some general guidelines are necessary.

Results decline when the number of operations performed falls below the minimum requirement and there is then an inverse ratio of mortality to numbers of operations performed. This is generally true below an annual rate of 200 operations, as noted in the survey by the Society of Thoracic and Cardiovascular Surgeons of Great Britain and Ireland (J Darke, 1979, personal communication).

Taking into account this figure of a minimum 200 open-heart operations per year quoted from the United States,[8] and the figure of 500 to 550 open-heart operations per year for a centre with four surgeons quoted in the World Health Organisation Report on 'Long term effects of coronary bypass surgery',[4] the committee considers three or four consultant surgeons or whole-time equivalents and their teams could achieve approximately 600 open-heart operations annually. This figure would determine the overall staffing of the centre and serve a population of between 2·5 and 3·5 million at the present rate of referral and surgical treatment, though if the expected levels of demand are reached such a centre would serve only an appreciably smaller community.

It is fully recognised that excellent work is being carried out at established units with a smaller turnover. Such units should be encouraged to expand. Those that have too small an annual turnover (that is, less than 200) to guarantee satisfactory results should not work in isolation and should whenever possible merge to form larger centres. The committee strongly recommends that excellent existing centres should not be denied resources to enable them to increase their output.

Principles of staffing

Adequate staffing at all levels to ensure a 24-hour medical, surgical, and investigational service is essential. The junior medical and surgical staff present a particular problem as they are in training and they must not be subjected to unremitting service work. Full days in the wards and operating theatres should not be followed by long hours on duty involving intensive care at night, which at present is a common pattern, leading to excessive fatigue, impaired clinical efficiency, and a reduction of time spent in teaching and research.

The committee is aware of the conflict of interests inherent in both providing an adequate career structure, which entails restrictions on the number of training posts, and ensuring that the number of trainees is sufficient to carry out the duties required. The problem is intensified at cardiac centres where the need to promote and undertake research programmes would inevitably entail larger numbers of staff. The frequent arrangement whereby service work is done largely by registrars who have limited opportunities for research, while research is done by research fellows who have only a restricted opportunity for routine clinical work that is essential for their training, is undesirable. The difficulty might be reduced if more consultant posts were made available to reduce the load on the junior staff.

The training programme for senior registrars should be designed to lead to progressive independence within the units so that in their final year they can accept total clinical responsibility. The number of senior registrars will be subject to some restriction because of limitations in the career prospects but provision must be made to meet service needs and training requirements and provide opportunities for research. Thus, since it may not always be possible for every cardiac centre to have established senior registrars, attachments of personnel from overseas and in research appointments should be encouraged.

A house officer programme should be developed for both house physicians and house surgeons. In order that junior staff structure may be related to career prospects, rotating training programmes at all levels would be advantageous.

(A) MEDICAL STAFFING

Broadly viewed, there are two types of cardiologist: the specialist who works in a combined centre and does little general medical work and the general physician with expertise in cardiology who works in a district, general, or other hospital, but does not carry out complex cardiological investigations of an invasive nature.[9] The requirements of staff and equipment for hospitals without a cardiac centre are described elsewhere in this report and the need for close liaison between general physicians with this interest and the staff of the cardiac centre is emphasised. The equivalent of six whole-time consultant cardiologists would be needed in a cardiac centre, the exact number depending on the degree of involvement of radiologists in invasive techniques such as cardiac catheterisation. It is envisaged that two of the six would have special expertise in the problems of instrumentation. There should be at least one established post for a senior cardiological registrar who might be supported by others from overseas, from general medical rotations, and from university appointments. It is expected that in a number of cardiac centres there will be facilities for paediatric cardiology, including infants and neonates. In these centres extra staff may be required but in any event it is anticipated that the appropriate consultant cardiologist will be able to deal with the cardiological problems of children (see section on paediatric cardiology). There should be appropriate registrars and senior house officers, their number depending on the needs of service, training, and the opportunities for research, all of which should be considered in relation to career prospects.

(B) SURGICAL STAFFING

The committee considers that in a cardiac centre three (or four) consultant surgeons, with a minimum of three whole-time equivalents, are needed to allow for the demands of emergency work, leave, sickness, teaching, and research in addition to the routine care of patients (see p. 213). Facilities should be available for each surgeon and his team to perform four to six open-heart operations a week, with additional time for emergencies. In cardiac centres dealing with paediatric cardiac surgery the number of surgeons would have to be adjusted (see section on paediatric cardiology).

Junior staffing structures as above must be related to service needs, training requirements, and research opportunities, as well as to career prospects, as in the case of the cardiologists. For a cardiac centre carrying out 10 to 15 open-heart operations a week the committee recommends one established senior registrar or equivalent, two registrars or equivalent (at least one of whom is in a general surgical training programme), two or three senior house officers, and, where appropriate, preregistration house officers. Because of the limitations in the number of junior medical staff more use might be made of the services of paramedical personnel.

Supporting services

The burden of cardiology and cardiac surgery on all supporting services is heavy and the staffing must be sufficient to provide 24-hour cover. The following recommendations are deliberately given in general terms because the actual number of personnel will vary with each centre.

(A) NURSING SERVICES

Nursing requirements will be exceptionally heavy. A high ratio of nurses to patients is to be expected throughout the unit, particularly in the intensive care areas. Nurses will be required to work not only in the wards and operating theatres but also in the cardiac catheterisation and angiocardiographic laboratories. It is expected that the medical and surgical intensive care areas will deal not only with postoperative patients and surgical emergencies but also with the acute problems of myocardial infarction and arrhythmias.

(B) CARDIOLOGICAL, RADIOLOGICAL, AND TECHNICAL SERVICES

Cardiac catheterisation laboratories should be adequate to allow for 40 to 50 cardiac investigations a week as well as providing a 24-hour service. One laboratory would not be enough. The technicians will be required to work on a rotational basis in the non-invasive investigational laboratory undertaking electrocardiography and echocardiography, and also in the cardiac pacing laboratory. A co-ordinated overall programme for medical and surgical technicians in the various departments is desirable.

(C) OTHER SERVICES

Other essential services in the cardiac centre, such as radiology, anaesthetics, intensive care, pathology, biochemistry, blood transfusion, perfusion, nuclear medicine, and immunology must be available. Details of equipment and personnel must be decided in consultation with the appropriate specialists.

Competition for resources

A combined cardiac centre, sited as it should be in the environment of a general hospital, competes with other disciplines for manpower, space, and resources.

A cardiac centre must be a regional, or preferably supraregional responsibility. It should receive directly earmarked funds allocated on a national basis. Competition for funds at district level must be avoided.

The insistence that every medical school should have a cardiac centre is unrealistic. It may well be that teaching interest and efficiency would best be served by combining cardiac departments of several medical schools to form a cardiac centre (see section on the special position of the London teaching hospitals).

Research

In the rapidly expanding field of cardiology, advances can only be made against a background of research activity.

(A) CLINICAL RESEARCH

Some activities must inevitably take the form of clinical research involving documentation of surgical results, pre- and postoperative haemodynamic and angiocardiographic studies, and similar projects. Such relatively straightforward studies now require the facilities for computer storage and retrieval of data.

(B) BASIC RESEARCH

In addition, it is vital that basic experimental cardiovascular research should be undertaken. Much of this work will inevitably require facilities for animal experimentation.

An active research programme is dependent upon a busy and effective practice and should be envisaged in each unit. Adequate space and facilities must therefore be made available. Contracts for consultant staff should, where required and appropriate, include sessions for research.

Monitoring of results of cardiac investigations and surgical operations

Experience has indicated the necessity of annual assessment of results so that standards can be maintained and improved, as emphasised by Brewer *et al.*[10] The Society of Thoracic and Cardiovascular surgeons in this country is already undertaking annual surveys. The committee recommends such reviews.

Teaching

Staff should participate in an integral teaching programme of a general or university hospital and exchange arrangements should be made with other centres. In particular, there should be liaison between cardiologists in the cardiac centre and those working elsewhere (see section on requirements for a cardiac department not in association with a cardiac centre).

Special position of London teaching hospitals

The recommendations in the present report describe what is intended to be a prototype of an ideal unit for medical and surgical care of heart disease at all ages.

The difficulty in applying these recommendations to the London teaching hospitals arises from the ratio of the number of teaching hospitals to the population they serve as well as from the competition from other disciplines for facilities and support. However, in some instances referrals for investigation and treatment come from other regions, thereby increasing the catchment area. Thus the four centres which would otherwise currently be appropriate to London's population of 10 million would not be sufficient. However, at present there are too many units in London, doing too little work, and unable to expand for physical and economic reasons. The number should be reduced, possibly by combining two or more units to form a large, more viable, and economic cardiac centre, serving more than one hospital. In order to ensure the workload envisaged, extra funds from regional or supraregional sources would be needed (see page 215). Undergraduates and resident staff from parent hospitals should have access to the cardiac centre and thus be exposed to the benefits of training in cardiac medicine and surgery.

Paediatric cardiology and paediatric cardiac surgery

Eight per thousand babies born suffer from congenital heart disease, of whom five require surgical treatment at some time. Many of these operations are already performed during the first year of life and this proportion is likely to increase in parallel with advances in medical and surgical management (D C Fyler, 1978, personal communication).

Many of these infants are seriously ill and need expert investigation in a special centre equipped with full diagnostic and surgical facilities which are available 24 hours a day. Though these infants can be transported considerable distances to the special centre, once investigation has taken place surgical action tends to be required quickly. In assessing the need of these infants the data from the New England Regional Infant Cardiac Programme have proved invaluable.[11–13] From these figures and from the Joint Committee on Higher Medical Training and Joint Committee on Higher Surgical Training,[14] 1400 (29 per million population) infant catheterisations and 850 infant operations, of which 425 (8·5 per million population) would be undertaken under cardiopulmonary bypass, can be expected from England and Wales each year.[14] However, data that we have been able to obtain from this country suggests that a large proportion of neonates with severe heart disease are neither investigated nor treated.

Even if all infants were adequately treated, it is clear that management on a strictly regional basis would not be appropriate. The argument for concentrating care for this high risk age group is extremely strong. It is unreasonable to expect a cardiac surgeon to maintain and improve standards of infant open-heart surgery unless he carries out on average at least one such operation a week. To provide cover throughout the year at least two such surgeons per centre are necessary. It follows that the number of centres necessary in England and Wales for infant cardiac care should be smaller than at present, certainly under 10. This would also ensure the best use of available resources and skills.

It would be both impractical and undesirable for such supraregional centres involved in investigation and surgery in infants to concentrate wholly on this age group. There would be an insufficient total volume of work, and what work there was would be so complex as to make impossible demands on the personnel of such a unit. It is essential that a centre for infant cardiac care should be an integral part of a larger unit dealing with a much wider range of patients. The specific needs of emergency cardiac catheterisation and infant operations within that unit would require two consultant cardiothoracic surgeons and two or three consultant paediatric cardiologists, all of whom would also be involved either in the cardiological or general paediatric care of the older patients. The cardiac centre for infants and children should be sited in association with a children's department with appropriate paediatric staff to care for the general needs of the patients.

The need for additional members of the medical and paramedical teams has already been outlined. Senior registrars in cardiology and cardiac surgery should rotate through these centres. Special arrangements should be made for the further training of those wishing to specialise in paediatric cardiology and cardiac surgery. Nursing staff must be trained in paediatrics and the nurse patient ratio should be even higher than for adults. Cardiac investigation for infants requires special equipment which must be available. Ready access to other paediatric specialities is also essential. All senior registrars in paediatrics should have training in paediatric cardiology, but not necessarily in a supraregional centre.

Screening of neonates and infants for cardiac disease is largely carried out by general paediatricians, and should continue to be so, though this will clearly mean that the cardiologists in supraregional centres will have to accept an important educational role. Senior registrars in paediatrics should have experience in infant cardiology in a supraregional centre.

Such a concentration of facilities obviously raises problems of travel for patients and their relatives, but the committee feels that these are acceptable in the best interests of these sick infants. Naturally, long-term follow-up of such patients is essential but, where distances are excessive, this can, at present, be arranged locally. The committee is aware of the disadvantages of separation of the child and family by long distances.

In making these recommendations, the committee stresses that recognition as a supraregional centre should be based not just on present workload and geographical location, but also on the quality of the work done.

Units of proven distinction should not suffer at the expense of rationalisation even though this principle is the logical guideline for the future. Small centres might be encouraged to merge resources as recommended for adults (see size of the unit and workload). The most important obstacle at present to mergers is the fear that the same inadequate facilities will be shared by more people. Thus adequate finance for neonates and paediatric work in the supraregional centres selected must be guaranteed.

If it is assumed that 40 per cent of patients with congenital heart disease presenting beyond infancy will require open-heart surgery, about 1700 (open), 500 (closed) heart operations, and 3800 cardiac catheterisations will be required in England and Wales each year in addition to those for infants already quoted. Bearing in mind the suggested workload for a general combined medical and surgical unit, it is clear that the supraregional centres as proposed above could deal with the majority of patients with congenital heart disease in this country. However, it would be important not to concentrate all facilities for older children with heart disease within the supraregional infant centres, because this would lead to a decline in local cardiological services and advice available to them. Furthermore, by no means all heart disease in children is congenital. Some patients would clearly be better treated, within combined cardiac centres described elsewhere, by consultants with appropriate training in infant cardiology who would probably combine this with adult work.

In view of the important part played by the general paediatrician in the management of much congenital heart disease at all ages particularly that not requiring surgery in the immediate neonatal period, it is important to have close liaison and ready access to the cardiac centre. Those staffing the cardiac centre should be aware of their responsibility for the cardiological training of general paediatricians and this responsibility should be reflected in the senior registrar training programme.

Thoracic surgery

While it is desirable that thoracic surgery (pulmonary and oesophageal) should be practised alongside cardiac surgery in the special centres, this may not always be possible. Some existing cardiac centres have the facilities for both thoracic and cardiac surgery, others do not.

The committee believes that there should be no rigid rules but wherever possible adequate facilities should be made available for cardiac and thoracic surgery in the same centre.

Requirements for a cardiac department in a hospital not having a cardiac centre

Such departments should be expected to deal with a wide variety of cardiovascular disease. Each department should, therefore, have at least one physician with a special interest and expertise in cardiology who could be in charge of the coronary care unit, the electrocardiographic department and, where available, the echocardiographic department. The value of other general physicians, whose special interests lie outside cardiology, having some special training in electrocardiographic interpretation (especially of arrhythmias) and in the care of acute cardiac emergency, is emphasised.

A cardiac department should include a coronary care ward with a minimum of four beds, preferably adjacent to and staffed by nurses from an acute general medical ward. If less than four beds are available, the coronary care ward should be part of the intensive care ward. The exact number of beds available for patients with cardiac disease will vary with the size of the hospital and population served. There should be facilities for the implantation of temporary pacemakers but the insertion of permanent pacemakers and pacemaker maintenance should usually be carried out in the nearest cardiac centre. In certain circumstances where the special interests and experience of the staff warrant it, the cardiac department of a general hospital could be organised to carry out the insertion and maintenance of permanent pacemakers and thus act as a subsidiary centre for this purpose. If two physicians on the staff have special experience in cardiology, the subsidiary centre could also concentrate expertise on echocardiography and special studies of arrhythmias by modern techniques. Close liaison should be maintained between such a subsidiary centre and both the cardiac centre and other general hospitals in the neighbourhood. The designation of certain general hospitals as subsidiary centres would avoid the disadvantages of transporting elderly and fragile patients long distances to a cardiac centre for maintenance of pacemakers. There should be an adequate electrocardiographic department including facilities for exercise testing. Methods of continuous 24-hour recording of the electrocardiogram should be available for the study of arrhythmias and disturbances of conduction. Provision of equipment for echocardiography is highly desirable provided that expertise is available. A special clinic for the management of hypertensive disease is to be recommended where the special interests of the physician warrant this. Facilities for simple rehabilitation after acute cardiac illness should be available and a clinic for the supervision of pregnant patients with heart disease is advisable. Research and teaching appropriate to these facilities and, where desirable, in collaboration with the cardiac centre is to be encouraged.

These recommendations envisage that cardiovascular research will also be carried out in academic, university, and other departments not necessarily connected with cardiac surgery. These departments will require special consideration.

The hazards of carrying out invasive investigations in laboratories divorced from a general hospital where emergency cardiac surgery is not available have already been pointed out.[15] In recent years, however, these dangers have been minimised mainly by the appreciation that investigations such as coronary arteriography should only be carried out by those who are expert and specially trained in the technique. It is advised that all new cardiac laboratories planned for invasive investigations should be sited within the same complex where cardiac surgery will take place, but it is realised that there are a number of existing laboratories that do not meet these criteria for geographical and other reasons, but in all cases known to the committee special and satisfactory arrangements have been made to overcome these difficulties.

Future review

In view of the rapid developments and changes in cardiovascular medicine and surgery, the report should be reviewed in not more than five years by a joint committee of the Royal College of Physicians and Royal College of Surgeons, and thereafter as recommended.

Members of the Joint Committee to Review the Joint Report of the RCP and RCS: 'A Combined Medical and Surgical Unit for Cardiac Surgery'.

ROYAL COLLEGE OF PHYSICIANS: J F Goodwin (chairman); R W Emanuel (hon. secretary); K E Jefferson (died 23 October 1977); D G Julian; N Conway; R Balcon; F J Macartney.

ROYAL COLLEGE OF SURGEONS: J L Collis; W P Cleland; P B Deverall; L D Abrams; C Drew.

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Br Heart J 1980; **43:** 220–225

Haemodynamic effects of oral salbutamol alone and in combination with sublingual isosorbide dinitrate in patients with severe congestive cardiac failure

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SUMMARY To examine possible augmentation of the effects of isosorbide dinitrate by salbutamol, haemodynamic measurements were made in 10 patients with severe chronic congestive cardiac failure who received isosorbide dinitrate 2·5 to 25 mg sublingually and salbutamol 4 to 12 mg orally, alone and in combination.

Isosorbide dinitrate reduced mean left ventricular filling pressure from 29 to 18 mmHg and increased mean cardiac index from 1·7 to 2·0 l/min per m², with no significant change in mean heart rate. Systemic arterial mean pressure fell from 85 to 72 mmHg.

Salbutamol increased cardiac index from 1·8 to 2·2 l/min per m². There was no significant change in left ventricular filling pressure, heart rate, or systemic arterial pressure.

Compared with control, combined isosorbide dinitrate and salbutamol reduced left ventricular filling pressure from 27 to 19 mmHg and increased cardiac index from 1·8 to 2·7 l/min per m², with no significant change in heart rate. Systemic arterial pressure fell from 82 to 75 mmHg.

The reduction in left ventricular filling pressure by combined treatment was similar to that produced by isosorbide dinitrate alone, but the increase in cardiac index was significantly greater than that produced either by isosorbide dinitrate alone or salbutamol alone.

Combined sublingual isosorbide dinitrate and oral salbutamol have an additive effect in improving left ventricular performance in patients with severe chronic congestive cardiac failure.

Intravenous salbutamol has been shown to be effective in improving left ventricular function in patients needing circulatory support after open-heart surgery[1] and in patients with chronic congestive cardiac failure.[2] Since salbutamol is predominantly a beta$_2$-adrenergic agonist, its effect in improving cardiac function is presumably mediated principally through a reduction in left ventricular afterload.

Isosorbide dinitrate is also effective in improving left ventricular function in congestive cardiac failure,[3–6] principally through preload reduction resulting from venodilatation. Combined salbutamol and isosorbide dinitrate treatment may, therefore, have an additive effect on the performance of the failing left ventricle.

This study was performed to determine the haemodynamic effects of oral salbutamol and sublingual isosorbide dinitrate, alone and in combination, in patients with severe congestive cardiac failure, in an attempt to establish such a combination as a possible form of long-term oral treatment.

Received for publication 30 April 1979

Patients and methods

Ten patients were studied, nine men and one woman, aged between 46 and 72 years. All were admitted to hospital because of severely incapacitating dyspnoea (grade III or IV, NYHA). In nine patients there was a long history of congestive cardiac failure secondary to ischaemic heart disease (seven patients) or probable alcoholic cardiomyopathy (two patients), while one patient had had an anterior myocardial infarction seven days previously (Table 1). One patient had had a permanent pacemaker implanted for chronic complete heart block; this patient was in a paced rhythm throughout the study. All patients had clinical and radiographic evidence of severe congestive heart failure. The clinical state of four was such that initial intensive treatment with intravenous inotropic agents and vasodilators was necessary. One patient was admitted in pulmonary oedema which improved with intravenous diuretic therapy. All patients had been treated with large doses of oral diuretics and one patient was taking digitalis.

On the day of the study the patients had received their normal dose of diuretics at least four hours before the study. Digitalis was withdrawn 24 hours before. At the time of the haemodyamic study the patients were judged to be clinically and haemodynamically stable, no inotropic or vasodilator agent having been administered within six hours of the start of the study. Informed consent was obtained in all cases.

A flow-directed thermodilution catheter was introduced into a subclavian vein percutaneously using a Desilets-Hoffman cannula and advanced to the pulmonary artery. In nine patients a first-pass radionuclide left ventriculogram was obtained.[7] In nine patients systemic arterial pressure was obtained by cuff measurement (two patients) or by cannulating the radial artery with a 20 gauge Medicut (seven patients); in one patient the systemic arterial systolic pressure only could be obtained by cuff measurement. Pressures were measured using Bell & Howell transducers and displayed on a Roche 144 portable monitor. The transducers were set for zero at mid-chest level. Cardiac output was measured by the thermodilution technique,[8] each estimation being performed in triplicate.

After control measurements of heart rate, systemic arterial pressure, pulmonary arterial pressure, pulmonary artery wedge pressure (or pulmonary arterial end-diastolic pressure), and cardiac output, isosorbide dinitrate (Cedocard, Cedona, Holland) was administered sublingually in doses of between 2·5 and 25 mg according to the individual response in left ventricular filling pressure (Table 1). Measurements were repeated after 15 minutes. A two-hour period was allowed for haemodynamic recovery[3] after which a second set of control measurements were made. Salbutamol 4 mg was then administered orally. If an increase in cardiac output was not observed at 30 minutes (each of the five patients who responded to 4 mg salbutamol did so at 30 minutes after administration), further doses were given until a response was seen (Table 1). To ensure a plateau had been reached in the response in cardiac output, cardiac output measurements were repeated after 30 minutes. The other haemodynamic measurements were then made, and all observations were repeated 15 minutes after isosorbide dinitrate given in the same dose as before.

Table 1 *Patient data*

Case no.	*Age (y)*	*Sex*	*Aetiology of heart failure*	*Dose of sublingual ISDN*	*Dose of salbutamol*
1	60	F	IHD	5 mg	4 mg
2	64	M	IHD	10 mg	4 mg
3	54	M	Cardiomyopathy	5 mg	4 mg
4	71	M	IHD (1 week after AMI)	5 mg	4 mg
5	63	M	IHD	5 mg	4 mg
6	60	M	IHD	15 mg	10 mg
7	59	M	IHD	25 mg	6 mg
8	59	M	IHD	5 mg	8 mg
9	72	M	IHD	2·5 mg	8 mg
10	46	M	Cardiomyopathy	15 mg	12 mg

AMI, anterior myocardial infarct; IHD, ischaemic heart disease; ISDN, isosorbide dinitrate

CALCULATIONS

Mean pulmonary arterial and pulmonary artery wedge pressures were obtained by electronic integration. When systemic arterial pressure was measured by arterial cannulation the mean values were obtained by electronic integration. When blood pressure was obtained by cuff measurement the mean was calculated using the formula:

$$\overline{AP} = D + (S-D)/3$$ [9]

where AP = arterial mean pressure (mmHg); D = diastolic pressure (mmHg); and S = systolic pressure (mmHg).

Left ventricular stroke work index (LVSWI) was calculated using the formula:

$$\text{LVSWI (g m per m}^2) = (\overline{AP} - \overline{PCWP}) \times \text{SVI} \times 0{\cdot}0136$$

where $\overline{PCWP}$ = pulmonary artery wedge mean pressure (mmHg), and SVI = stroke volume index (ml/m^2).

Systemic vascular resistance (SVR) was calculated using the formula:

$$\text{SVR (dynes s cm}^{-5}) = (\overline{AP}/\text{CO}) \times 80$$

where CO = cardiac output (l/min).

Statistical analysis was by the paired Student's t test.

Results

RADIONUCLIDE LEFT VENTRICULOGRAPHY

There was severe reduction in left ventricular ejection fraction associated with diffuse hypokinesis.

in all nine patients in whom radionuclide left ventriculography was performed.

HAEMODYNAMIC DATA (Table 2)
Effects of isosorbide dinitrate
There was no significant change in mean heart rate. The mean value for systemic arterial mean pressure fell from 85 to 72 mmHg (15%, $p<0\cdot01$). The mean value for pulmonary arterial mean pressure fell from 37 to 24 mmHg (35%, $p<0\cdot001$), while that for pulmonary artery wedge mean pressure fell from 29 to 18 mmHg (38%, $p<0\cdot001$). Mean cardiac index increased from 1·7 to 2·0 l/min per m^2 (18%, $p<0\cdot01$) and stroke volume index increased from 18 to 22 ml/m^2 (22%, $p<0\cdot01$). There was no significant change in mean left ventricular stroke work index. Mean systemic vascular resistance fell from 2593 to 1777 dynes s cm^{-5} (31%, $p<0\cdot001$).

Effects of salbutamol
There were no significant changes in mean values for heart rate or systemic arterial mean pressure. The mean value for pulmonary arterial mean pressure increased slightly from 35 to 37 mmHg (6%, $p<0\cdot05$) but there was no significant change in the mean value for pulmonary artery wedge mean pressure. Mean cardiac index increased from 1·8 to 2·2 l/min per m^2 (22%, $p<0\cdot001$). An increase was observed in all patients, except one in whom no change could be effected despite the administration of 12 mg salbutamol (in this patient a large increase in cardiac index was observed when isosorbide dinitrate was administered concurrently) (Fig. 1). After salbutamol mean stroke volume index increased from 20 to 23 ml/m^2 (15%, $p<0\cdot005$). Mean systemic vascular resistance fell from 2128 to 1748 dynes s cm^{-5} (18%, $p<0\cdot005$) while mean stroke work index increased from 15 to 18 g m per m^2 (20%, $p<0\cdot025$).

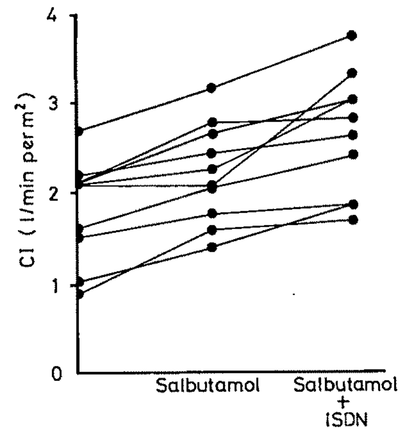

Fig. 1 *Effects of oral salbutamol on cardiac index (CI) in individual patients. ISDN, isosorbide dinitrate.*

Effects of combined salbutamol and isosorbide dinitrate
Compared with the second control period, combined salbutamol and isosorbide dinitrate produced no significant change in mean heart rate. Systemic arterial mean pressure fell from 82 to 75 mmHg (8%, $p<0\cdot01$). Pulmonary arterial mean pressure fell from mean 35 to 28 mmHg (20%, $p<0\cdot001$), while pulmonary artery wedge mean pressure fell from mean 27 to 19 mmHg (30%, $p<0\cdot001$). Cardiac index increased from 1·8 to 2·7 l/min per m^2 (50%, $p<0\cdot001$) and stroke volume index increased from 20 to 28 ml/m^2 (40%, $p<0\cdot001$). Left ventricular stroke work index increased from 15 to 22 g m per m^2 (47%, $p<0\cdot001$). Systemic vascular resistance fell from 2128 to 1326 dynes s cm^{-5} (38%, $p<0\cdot001$).

Effects of salbutamol plus isosorbide dinitrate vs isosorbide dinitrate alone
There was no significant change in mean heart rate with either isosorbide dinitrate alone or with the combination of salbutamol and isosorbide dinitrate, and there was no significant difference between the changes in systemic arterial mean pressure. The falls in mean values for pulmonary

Table 2 *Haemodynamic effects of isosorbide dinitrate and salbutamol alone and in combination*

	No. of patients	*Control 1*	*ISDN*	*Control 2*	*Salbutamol*	*Salbutamol plus ISDN*
Heart rate (beats/min)	9§	96 ±5·4	94 ±5·6	98 ±4·6	101 ±4·0	100 ±3·1
Mean systemic arterial pressure (mmHg)	9	85 ±4·0	72 ±2·1†	82 ±4·7	82 ±4·5	75 ±4·9†
Mean pulmonary arterial pressure (mmHg)	10	37 ±2·2	24 ±2·4‡	35 ±2·1	37 ±2·0*	28 ±1·9‡
Left ventricular filling pressure (mmHg)	10	29 ±1·8	18 ±1·9‡	27 ±1·6	27 ±1·4	19 ±1·1‡
Cardiac index (l/min per m^2)	10	1·7 ±0·2	2·0 ±0·2†	1·8 ±0·2	2·2 ±0·2‡	2·7 ±0·2‡
Stroke volume index (ml/m^2)	10	18 ±2·2	22 ±2·5	20 ±2·2	23 ±2·3†	28 ±2·5‡
Systemic vascular resistance (dynes s cm^{-5})	9	2593 ±328	1777 ±249‡	2128 ±249	1748 ±176†	1326 ±157‡
Left ventricular stroke work index (g m/m^2)	9	15 ±2·8	18 ±1·9	15 ±2·1	18 ±2·9*	22 ±1·1‡

All results are expressed as mean ±SEM.
ISDN, isosorbide dinitrate. *$p<0\cdot05$; †$p<0\cdot01$; ‡$p<0\cdot001$. §Data for patient with fixed heart rate (permanent pacemaker) omitted.

arterial mean pressure and pulmonary artery wedge mean pressure produced by the combination were similar to those produced by isosorbide dinitrate alone. Cardiac index increased to 2·0 l/min per m^2 with isosorbide dinitrate alone, but to 2·7 l/min per m^2 with the combination (35%, $p < 0·001$); the corresponding values for stroke volume index were 22 and 28 ml/m^2 (27%, $p < 0·001$) and for left ventricular stroke work index 18 and 22 g m per m^2 (22%, $p < 0·05$). The fall in systemic vascular resistance with the combination was similar to that occurring after isosorbide dinitrate alone.

Effects of salbutamol plus isosorbide dinitrate vs salbutamol alone

There was no significant change in mean heart rate with either salbutamol alone or the combination. Systemic arterial mean pressure remained at 82 mmHg with salbutamol alone, but fell to 75 mmHg with the combination (8%, $p < 0·02$). Pulmonary arterial mean pressure increased slightly to 37 mmHg with salbutamol alone but fell to 28 mmHg with the combination (24%, $p < 0·001$); the corresponding values for pulmonary artery wedge mean pressure were 27 and 19 mmHg (30%, $p < 0·001$). Cardiac index increased to 2·2 l/min per m^2 with salbutamol alone and to 2·7 l/min per m^2 with the combination (23%, $p < 0·005$); the corresponding values for stroke volume index were 23 and 28 ml/m^2 (22%, $p < 0·001$) and for left ventricular stroke work index 18 and 22 g m per m^2 (22%, $p < 0·001$). Systemic vascular resistance fell to 1748 dynes s cm^{-5} with salbutamol alone and to 1326 dynes s cm^{-5} with the combination (24%, $p < 0·005$).

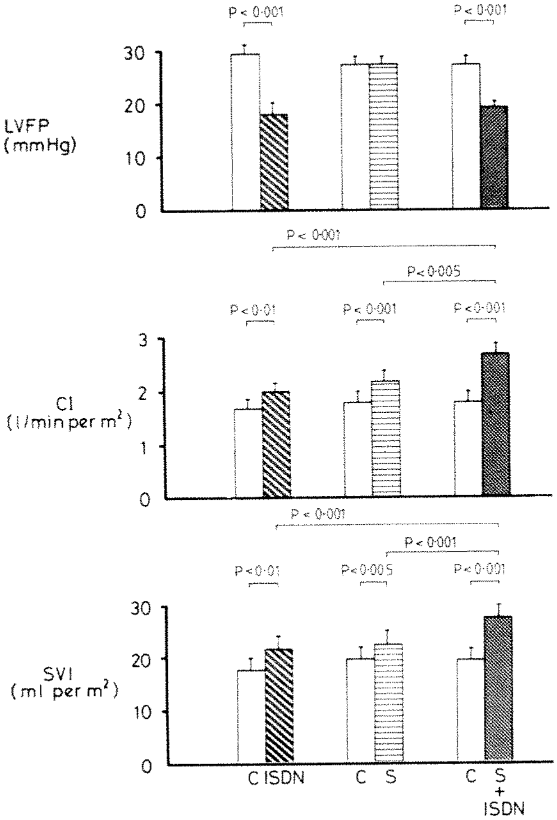

Fig. 2 *Effects of isosorbide dinitrate (ISDN) and salbutamol (S), alone and in combination, on mean values for cardiac index (CI), stroke volume index (SVI), and left ventricular filling pressure (LVFP). Bars indicate ± standard error of mean. C = control.*

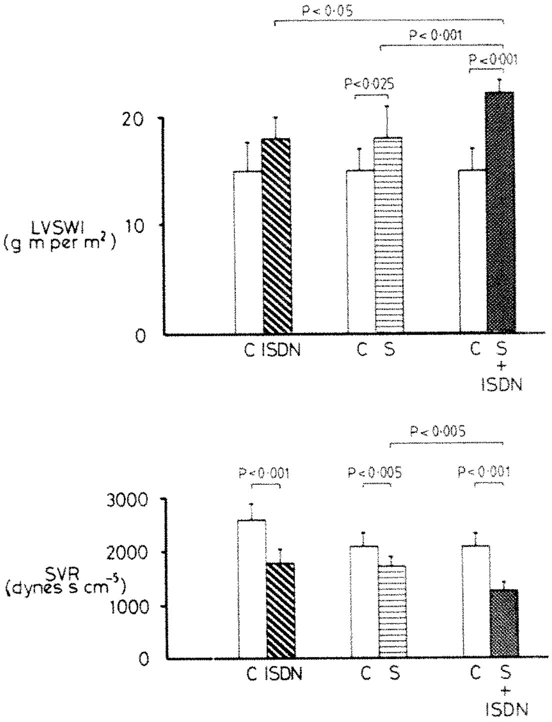

Fig. 3 *Effects of isosorbide dinitrate (ISDN) and salbutamol (S), alone and in combination, on mean values for left ventricular stroke work index (LVSWI), and systemic vascular resistance (SVR). Bars indicate ± standard error of mean.*

There were no unwanted effects of either drug, alone or in combination.

Changes in cardiac index, stroke volume index, left ventricular filling pressure, left ventricular stroke work index, and systemic vascular resistance are illustrated in Fig. 2 and 3.

Discussion

In the severely ill patient with advanced congestive cardiac failure, an increase in left ventricular filling pressure and depression of cardiac output represent the clinically important manifestations of impaired cardiac function. The former, by causing pulmonary venous hypertension, produces dyspnoea and may result in pulmonary oedema and arterial hypoxaemia, while the latter leads to reduced renal perfusion, with the consequent exacerbation of sodium and fluid retention. The primary therapeutic objectives in the management of such patients are thus reduction in left ventricular filling pressure and augmentation of cardiac output. In recent years these objectives have been achieved pharmacologically using intravenous vasodilators including sodium nitroprusside,[10] [11] inotropic agents such as dopamine[12] and dobutamine,[13] or a combination of vasodilator and inotropic agents.[6] [14]

The search continues, however, for a suitable non-parenteral preparation for the long-term management of patients with chronic congestive cardiac failure. From experience gained with parenteral agents it appears that an ideal oral agent or combination of agents would dilate arterioles and veins, effecting reductions in left ventricular afterload and preload, respectively, together with an inotropic action. The summation of these effects should act to augment cardiac output and reduce left ventricular filling pressure, ideally without producing side effects such as tachycardia, hypotension, or arrhythmias.

Salbutamol is primarily a beta$_2$-adrenergic agonist[15] [16] but has a cardiac stimulant effect (beta$_1$) albeit considerably less potent than isoprenaline.[17] Its beneficial effect in congestive heart failure may therefore be principally the result of a reduction in left ventricular afterload by arteriolar vasodilatation, as suggested by Wyse *et al.*,[1] or to an inotropic effect as suggested by Sharma and Goodwin,[2] or a combination of both. Isosorbide dinitrate has been shown to be effective in reducing left ventricular filling pressure in patients with congestive cardiac failure, with little or no change in resting cardiac output.[3] [4] These observations have been interpreted as showing a potent venodilating effect with a less important arteriolar vasodilating effect. The combined properties of salbutamol and isosorbide dinitrate, both available for oral use, therefore fulfil in principle the criteria outlined for the long-term management of patients with chronic congestive cardiac failure.

In this study the principal effect of salbutamol was to improve cardiac output and stroke volume. The failure of the drug to reduce left ventricular filling pressure may have been the result of a venoconstricting effect since adrenergic stimulation has been shown to produce venoconstriction in dogs,[18] though a recent study in man[16] showed no effect of salbutamol on forearm venous tone.

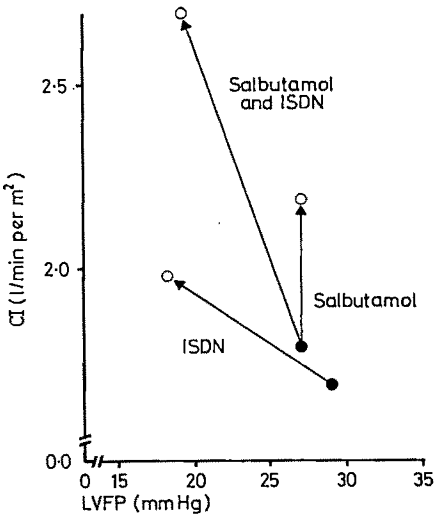

Fig. 4 *Effects of isosorbide dinitrate (ISDN) and salbutamol, alone and in combination, on the relation between left ventricular filling pressure (LVFP) and cardiac index (CI).*

In distinct contrast the principal effect of isosorbide dinitrate was to reduce left ventricular filling pressure. The observed haemodynamic effects of combined salbutamol and isosorbide dinitrate fulfilled the expectation of an additive effect in that there was a more comprehensive improvement in left ventricular performance than that produced by either agent alone (Fig. 4). This improvement was achieved without serious hypotension, tachycardia, or arrhythmias.

Oral salbutamol and sublingual isosorbide dinitrate appear to have a beneficial, additive effect in patients with severe, chronic congestive cardiac failure. Though the haemodynamic results of this study relate to the acute effects of such a combination they appear to establish this as a possible new therapeutic approach in the long-term management of such patients.

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Relation between isovolumic relaxation period of left ventricle and pulmonary artery pressure in d-transposition of the great arteries*

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SUMMARY The study aimed to identify the best echocardiographic time interval (systolic or diastolic) for assessing pulmonary artery pressure in children with d-transposition of the great arteries. Echocardiograms were performed in 21 children with d-transposition of the great arteries within 48 hours of cardiac catheterisation. None of the children had had a Mustard procedure. Twenty-four recordings were obtained, three patients having been catheterised twice. Highest correlations were found for the ratio of the isovolumic relaxation time over the ejection time of the left ventricle (IRT/LVET) to the systolic pressure in the pulmonary artery and also between IRT/LVET and the difference between mean pulmonary artery pressure and mean left atrial pressure. All patients with a negative IRT/LVET ratio had a pulmonary systolic pressure lower than 35 mmHg and a mean pulmonary pressure lower than 25 mmHg. In patients with d-transposition, a negative IRT/LVET ratio appears to be a reliable indication of normal pressure in the pulmonary circulation. Serial echocardiographic studies for the follow-up of patients with d-transposition should include measurement of the time of relaxation of the left ventricle.

The value of echocardiography in the assessment of the pulmonary vascular bed has been shown by several investigators using systolic time intervals (STI). Most studies have shown good correlation between pre-ejection period (PEP),[1] pre-ejection period over ejection time (PEP/ET),[2 3] isometric contraction time[4] of the right ventricle, and the pulmonary pressure of patients with normally related great arteries. More recently, Gutgesell[5] has used the ratio PEP/ET of the left ventricle to estimate pulmonary pressure in d-transposition of the great arteries.

Although the isovolumic relaxation time (IRT) of the right ventricle has long been shown to be a good index of pulmonary pressure,[6–8] the value of IRT of the left ventricle in d-transposition of the great arteries has not been studied. In addition, previous measurements of IRT in adults have involved the use of apex cardiograms which are difficult to obtain in small children.

Because of the clinical importance of establishing reliable criteria for evaluation of pulmonary artery pressure in d-transposition[9] and the ease with which mitral and pulmonary valve echograms are obtained in this condition, we have compared the reliability of IRT of the left ventricle to that of STI in the assessment of the pulmonary vascular bed.

Subjects and methods

Echocardiograms were performed in 21 children with d-transposition within 48 hours of a cardiac catheterisation. Twenty-four recordings were obtained, three patients having been catheterised twice. Patients ranged in age from 1 day to 5·5 years (median age: 21·5 months). As the peculiar variations of pressure in the newly formed left atrium[10] might influence the time of opening of the mitral valve, patients with an intra-atrial baffle (Mustard procedure) were excluded from the study. They will form the subject of another report. Six patients had an associated ventricular septal defect, four had pulmonary stenosis (gradients greater than

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*Work supported in part by the Macdonald Stewart Foundation, the Canadian Heart Foundations, and La Fondation Justine-Lacoste-Beaubien.

Received for publication 20 July 1979

15 mmHg), and five had ventricular septal defect and pulmonary stenosis. Patients older than 3 months were premedicated before cardiac catheterisation with a standard mixture of meperidine, promethazine, and chlorpromazine.[11] Pulmonary artery pressure was recorded in all patients before angiography.

Echocardiograms were recorded simultaneously with an electrocardiogram on a Smith Kline Ekoline 20A coupled with a Honeywell fibreoptic recorder (model 1856) or a Cambridge multichannel physiological recorder. Tracings were obtained at a paper speed of 100 mm/s with time lines at 40 ms allowing measurements to be made to the nearest 5 ms or better.[12] Aerotech 5 MHz unfocused and 3·5 MHz focused transducers were used, according to the size of the patient. Left ventricular time intervals were calculated according to the criteria previously published by Hirschfeld and co-workers.[2] The pre-ejection period was measured from the onset of ventricular depolarisation (beginning of the Q wave on the electrocardiogram) to the opening of the pulmonary valve. The ejection time was measured from opening to closure of the pulmonary valve. Isovolumic contraction time was taken as the difference between QP_0 (Q to pulmonary valve opening) and QM_C (Q to mitral valve closure). Isovolumic relaxation time was defined as the difference between QM_0 (Q to mitral valve opening) and QP_C (Q to pulmonary valve closure) (Fig. 1). Mitral opening was defined as the point where anterior and posterior mitral leaflets separated (point D) on the echocardiogram. All measurements were performed on cardiac cycles

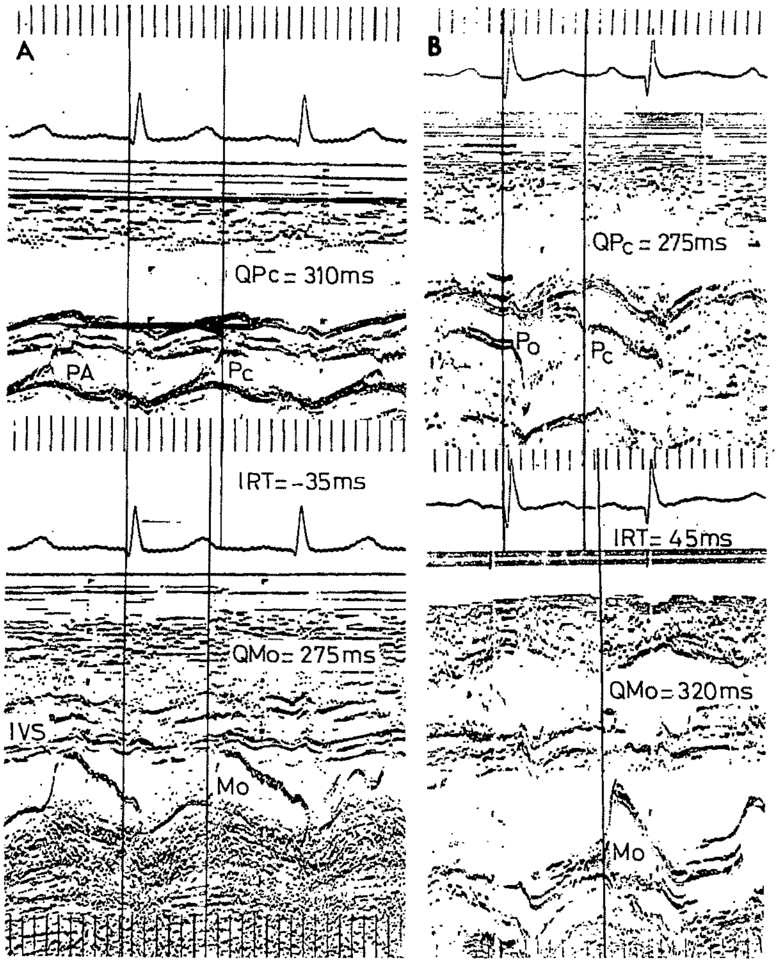

Fig. 1 *Echocardiograms of pulmonary and mitral valves of two children with d-transposition. Panel* A *demonstrates a negative IRT and panel* B *a positive IRT. PA, pulmonary artery; IVS, interventricular septum;* P_o*, opening of pulmonary valve;* QP_c*, interval from the beginning of the Q wave to closure of pulmonary valve;* QM_o*, interval from the beginning of the Q wave to opening of mitral valve;* $IRT = QM_o - QP_c$

Table 1 *Haemodynamic and echocardiographic data*

Age	*Associated lesions*	*PASP (mmHg)*	*PADP (mmHg)*	$\overline{PA}$ *(mmHg)*	$\overline{PA}$-$\overline{LA}$ *(mmHg)*	$\overline{PA}/\overline{Ao}$	*PEP/ LVET*	*ICT (ms)*	*ICT/ LVET*	*IRT (ms)*	*IRT/ LVET*
5 d*	VSD	49	26	33	23	0·58	0·23	–15	–0·08	10	0·05
19 mth		23	13	15	8	0·23	0·25	– 5	–0·02	–25	–0·11
26 mth		21	11	16	11	0·20	0·21	0	0·00	10	0·04
30 mth		22	10	15	6	0·25	0·14	0	0·00	–20	–0·07
2 d†	VSD	45	16	32	27	0·63	0·29	15	0·08	10	0·05
33 mth	PS	20	7	11	6	0·14	0·16	5	0·02	–15	–0·05
27 mth		22	10	13	5	0·19	0·17	–30	0·13	–20	–0·08
17 mth	PS	25	12	17	10	0·26	0·15	20	0·07	–25	–0·09
7 mth		22	10	14	4	0·18	0·20	0	0·00	–20	–0·07
2 mth	VSD	61	28	46	34	0·77	0·21	5	0·02	25	0·12
24 mth		36	11	20	14	0·33	0·20	0	0·00	20	0·10
24 mth		95	62	77	71	1·13	0·40	40	0·20	40	0·20
12 mth	VSD	87	46	65	57	1·05	0·34	30	0·15	45	0·22
1 d	VSD	68	37	41	35	0·077	0·30	20	0·10	30	0·15
30 mth	PS	22	10	16	6	0·26	0·25	30	0·11	–35	–0·13
30 mth		30	17	22	19	0·29	0·19	5	0·02	5	0·02
66 mth	VSD PS	29	17	23	2	0·32	0·18	*5	0·02	–30	–0·09
3 mth†	VSD PS	17	6	12	10	0·20	0·30	10	0·05	–15	–0·08
30 mth	VSD PS	29	11	20	15	0·32	0·14	20	0·07	–10	0·04
46 mth*	PS	30	14	17	9	0·24	0·35	20	0·09	–10	–0·04
6 mth	VSD PS	75	29	47	39	0·77	0·30	10	0·05	20	0·10
2 d†	VSD	60	5	31	26	0·58	0·25	0	0·00	10	0·06
8 mth†	PS	11	2	7	5	0·11	0·24	0	0·00	–20	–0·10
66 mth	VSD PS	32	12	20	13	0·32	0·16	10	0·01	–10	–0·03

* Catheterised twice. † Catheterised twice.

VSD, ventricular septal defect; PS, pulmonary stenosis; PASP, pulmonary artery systolic pressure; PADP, pulmonary artery diastolic pressure; $\overline{PA}$, mean pulmonary artery pressure; $\overline{LA}$, mean left atrial pressure; $\overline{Ao}$, mean aortic pressure; PEP, pre-ejection period; LVET, left ventricle ejection time; ICT, isovolumic contraction time; IRT, isovolumic relaxation time.

of equal RR intervals. Each value represented the average of at least five different complexes. All infants were either sleeping or resting quietly at the time of the echocardiogram.

To determine the best regression equations relating pulmonary pressure to STI and IRT, we used the 'stepwise multiple regression' technique.[13] This technique permits the inclusion of the echocardiographic variables that significantly increase the regression coefficient. The validity of the regression equations was assessed by Fisher's F test.

Results

Measurements obtained are given in Table 1. Correlation coefficients relating the left ventricular STI and IRT to haemodynamic data are shown in Table 2. IRT showed a better correlation than STI with all haemodynamic indices studied. Still stronger correlations were found when the ratio IRT/LVET was used.

The relation between IRT/LVET and the pulmonary systolic and mean pressures are shown in Fig. 2A and B. Negative IRT and IRT/LVET values were observed in 13 cases and were always associated with a peak pulmonary pressure of less than 35 mmHg and a mean pressure of less than 25 mmHg. The best planar and multiple regression equations are given in Table 3.

There was no relation between left ventricular systolic pressure and IRT.

Discussion

In d-transposition of the great arteries, IRT of the left ventricle is the time between closure of the pulmonary valve and opening of the mitral valve. As in subjects without d-transposition,[6 7 14] IRT should be influenced by: the level of pulmonary artery pressure at the time of closure of the pulmonary valve, left atrial pressure, heart rate, and downslope of left ventricular pressure, this last factor being dependent on preload, afterload, contractility, and compliance of the left ventricle.[15 16]

In pulmonary hypertension, the IRT will lengthen because pressure in the ventricle will fall from a higher point before reaching the left atrial level. The Q-P_c interval (from the beginning of the

Table 2 *Correlation matrix*

	PEP/ LVET	*ICT*	*ICT/ LVET*	*IRT*	*IRT/ LVET*
PASP	0·64	0·45	0·53	0·87	0·90
PADP	0·63	0·52	0·60	0·76	0·79
$\overline{PAMP}$	0·64	0·51	0·59	0·84	0·87
$\overline{PA}$-$\overline{LA}$	0·68	0·53	0·62	0·88	0·90
$\overline{PA}/\overline{Ao}$	0·64	0·48	0·56	0·86	0·89

See footnote to Table 1 for explanation of abbreviations.

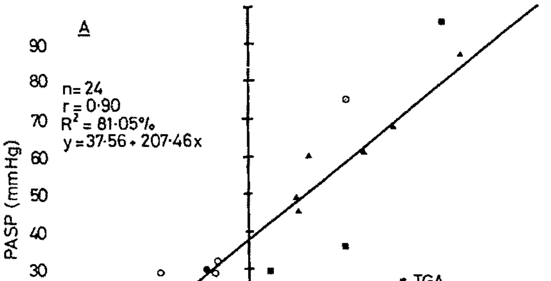

Fig. 2 *Relation between IRT/LVET, PASP* (A), *and PAMP* (B). *PASP, pulmonary artery systolic pressure; PAMP, pulmonary artery mean pressure; IRT, isovolumic relaxation time; LVET, left ventricle ejection time.*

Q wave to closure of the pulmonary valve) by itself does not influence the duration of the fall of ventricular pressure[6–8]. Therefore, conditions delaying closure of the pulmonary valve such as pulmonary stenosis or ventricular conduction delay should not interfere directly with IRT.

An increase in left atrial pressure causes the mitral valve to open early and thereby shortens IRT.[17] In patients with d-transposition of the great arteries and high pulmonary vascular resistance, raised pulmonary pressure should work together with low left atrial pressure to increase IRT. The reverse is true in patients with low pulmonary resistance and high atrial pressure. In d-transposition, since most patients have a large atrial septal defect, variations of left atrial pressure secondary to variations of pulmonary blood flow should be smaller. In fact, the correlation coefficient was only slightly higher for IRT when the left atrial mean pressure was subtracted from the pulmonary artery mean pressure (Table 2).

We found a weak correlation ($r = -0{\cdot}46$) between IRT and heart rate, as has been found by others in subjects without d-transposition[15–18] and in experimental studies in dogs.[17]

The influence of the downslope of left ventricular pressure on IRT is more difficult to evaluate. In dogs, experimental hypertrophy of the right ventricle induced by pulmonary artery banding resulted in a decreased right ventricular contractility and compliance.[19] Increased afterload, decreased preload, and left ventricular contractility have also been found to prolong IRT. Drugs can also influence IRT by acting on myocardial contractility.[18] The relative importance of these factors on IRT, through their influence on left myocardial con-

Table 3 *Regression equations*

Variable	*Type of regression*	*Regression equation*	*R²%*	*s*	*Fisher's F test*
PASP (mmHg)	Multiple	(PASP) =22·62+638·70 (IRT/LVET) −2·08 (IRT)+164·90 (PEP/LVET)²	90·3	7·81	62·34 P<0·005
	Planar	(PASP) =37·56+207·46 (IRT/LVET)	81·1	10·42	94·12 P<0·005
PADP (mmHg)	Multiple	(PADP) =12·69+76·31 (IRT/LVET)+784·13 (ICT/LVET)²	83·3	6·03	52·37 P<0·005
	Planar	(PADP) =11·03−65·67 (IRT/LVET)+620·52 (IRT/LVET)²	80·0	8·01	25·12 P<0·005
PAMP (mmHg)	Multiple	(PAMP) =19·30−361·23 (IRT/LVET)+613·49 (ICT/LVET)² − 1·06 (IRT)	89·2	6·21	54·88 P<0·005
	Planar	(PAMP) =25·35+151·34 (IRT/LVET)	76·4	7·88	46·91 P<0·005
$\overline{PA}$-$\overline{LA}$ (mmHg)	Multiple	($\overline{PA}$-$\overline{LA}$) =14·30−125·46 (IRT/LVET)+690·07 (ICT/LVET)²	90·8	5·57	103·89 P<0·005
	Planar	($\overline{PA}$-$\overline{LA}$) =18·03+155·21 (IRT/LVET)	80·7	6·68	68·90 P<0·005
$\overline{PA}$/$\overline{Ao}$	Multiple	($\overline{PA}$/$\overline{Ao}$) = 0·09+8·12 (IRT/LVET) − 0·03 (IRT)+1·06 (PEP/LVET)	888·1	0·11	62·81 P<0·005
	Planar	($\overline{PA}$/$\overline{Ao}$) = 0·41+2·54 (IRT/LVET)	78·8	0·11	49·36 P<0·005

See footnote to Table 1 for explanation of abbreviations. R²%, percentage of the variation explained; *s*, standard deviation of residuals.

tractility, obviously cannot be determined in the group of patients studied. One would think that patients with d-transposition of the great arteries and pulmonary stenosis would have hypertrophic and 'non compliant' left ventricles with a prolonged IRT. However, this effect, if present, does not seem to be significant enough to change, in our group of patients, the correlation between IRT/LVET ratio and the pulmonary artery pressure.

A negative IRT was found in most cases of d-transposition of the great arteries with normal pulmonary pressure. Echocardiographic identification of the point of opening of the mitral valve could in part explain this finding. Pohost *et al.*[20] in dogs and Rubenstein *et al.*[21] in humans have distinguished point D and point D′; point D located at the separation of anterior and posterior mitral leaflets and point D′ marking the onset of the rapid anterior movement of the mitral valve. This latter point correlated better with haemodynamic indicators of mitral valve opening defined as the crossover point between left atrial and ventricular pressures. However, more recently Tsakiris *et al.*[22] showed with dogs that mitral valve opening consistently preceded the diastolic crossover point. Furthermore, in children, the distinction between point D and D′ is difficult, probably because of the rapid heart rate and of the high velocity of mitral valve opening. For these reasons, we have taken the point of separation of anterior and posterior mitral leaflets as representing opening of the valve. The prolonged "hang-out" time of the pulmonary valves in cases of d-transposition with low vascular resistance and increased pulmonary flow could also be put forward to explain the negative IRT in these patients.

Higher correlations appear to exist between pulmonary artery pressure and diastolic rather than systolic time intervals, the highest correlation coefficient being found between pulmonary artery systolic pressure and the ratio IRT/LVET ($r=0{\cdot}9$). With systolic time intervals the best correlation was between PEP/LVET and mean pulmonary pressure minus mean left atrial pressure ($r=0{\cdot}68$). As for the correlation of the ratio PEP/LVET and pulmonary artery diastolic pressure, r was found to be 0·63 (compared to 0·70 in Gutgesell's work.[5]

Good correlation (0·9) was also found between IRT/LVET and the ratio of mean pulmonary over mean aortic pressure. This correlation has also been noted for STI, though to a lesser degree.[5]

In patients with d-transposition of the great arteries, frequent assessment of the pulmonary vascular resistance is of considerable clinical importance. In such patients, the risk of pulmonary arteriolar changes has been well documented, not only in the presence of ventricular septal defect[9] but also with an intact septum[23] and even after surgical correction by the Mustard procedure.[9 24] From our present report, it can safely be stated that in patients with d-transposition of the great arteries a negative IRT/LVET ratio is a reliable index of normal pressure in the pulmonary circulation. Serial echocardiographic studies for the follow-up of patients with d-transposition should, therefore, always include measurement of the time of relaxation of the left ventricle in addition to currently used STI.

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Br Heart J 1980; 43: 232–236

Non-invasive diagnosis of a false left ventricular aneurysm by echocardiography and pulsed Doppler echocardiography

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SUMMARY This report describes the diagnosis of a false left ventricular aneurysm by echocardiography and pulsed Doppler echocardiography. The patient successfully underwent resection of the pseudoaneurysm.

A diagnosis of a false left ventricular aneurysm and its differentiation from a true aneurysm is important for the treatment and prognosis of this uncommon disorder.

Pseudoaneurysms usually develop when blood perforates the left ventricular wall forming a chamber contained by blood, thrombotic material, and pericardial tissue. The main cause of false aneurysms is myocardial infarction (Hurst *et al.*, 1963; van Tassel and Edwards, 1972). Unlike true aneurysms false aneurysms have a tendency to early and late rupture, necessitating early diagnosis and prompt surgical intervention (Vlodaver *et al.*, 1975).

Echocardiography and nuclear medicine are well-recognised diagnostic tools for detecting a pseudoaneurysm (Roelandt *et al.*, 1975; Botvinick *et al.*, 1976; van Mechelen *et al.*, 1978). However, echocardiography is not able to differentiate the false aneurysm from a local haematoma, a pericardial cyst, a diverticulum, or a pericardial effusion, or from a true aneurysm. Only the demonstration of the small connection between the ventricular cavity and the aneurysm by angiocardiography could confirm the diagnosis.

In this report we describe a case of a large posteroinferolateral false aneurysm, which had been suspected by echocardiography and confirmed by angiocardiography, pulsed Doppler echocardiography, and cardiac surgery.

Case report

A 59-year-old man had been admitted to his local hospital in March 1974 with an inferior myocardial wall infarction.

This diagnosis was established by typical electrocardiographic and enzyme changes. Before this event he had never been in a hospital and he denied symptoms or signs suggestive of coronary artery disease. The patient's hospital course was uneventful and after 3 weeks he was discharged without medication. He was free of symptoms and did not see a doctor until May 1978 when he felt his heart beating irregularly. He was then admitted to our institution with a fast irregular heart rate between 80 and 120 beats/min and an arterial blood pressure of 170/100 mmHg. No peripheral oedema or venous congestion was noted, and no praecordial heave or apical impulse was felt.

On auscultation a fourth heart sound was heard but no other systolic or diastolic extra sound or murmur could be detected. The electrocardiogram showed atrial flutter with varying atrioventricular block. Q waves were present in leads II, III, aVF, and V6, terminal negative T waves in III and a VF, with ST segment elevation in II and III. This electrocardiogram was interpreted as showing an old inferolateral myocardial infarction and possible aneurysm.

The chest *x*-ray film showed dilatation of the heart. In the lateral view there was a large posterior bulge of the left ventricle with narrowing of the retrocardiac space.

After echocardiographic studies were performed, the patient underwent cardiac catheterisation with angiocardiography, and then successful cardiac surgery with resection of the pseduoaneurysm.

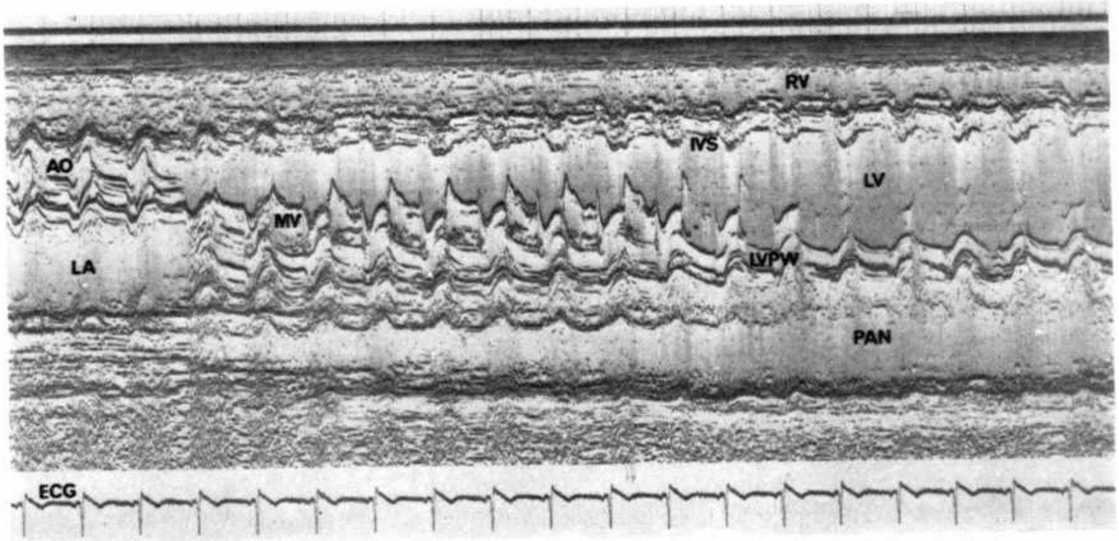

Fig. 1 *Preoperative condensed M-mode scan from the aorta (AO) towards the left ventricle (LV). At the atrioventricular junction an echo-free area is recorded (PAN) behind the posterior left ventricular wall (LVPW) extending from the left atrium (LA) to the left ventricle. MV, mitral valve; RV, right ventricle; IVS, interventricular septum; PAN, false or pseudoaneurysm.*

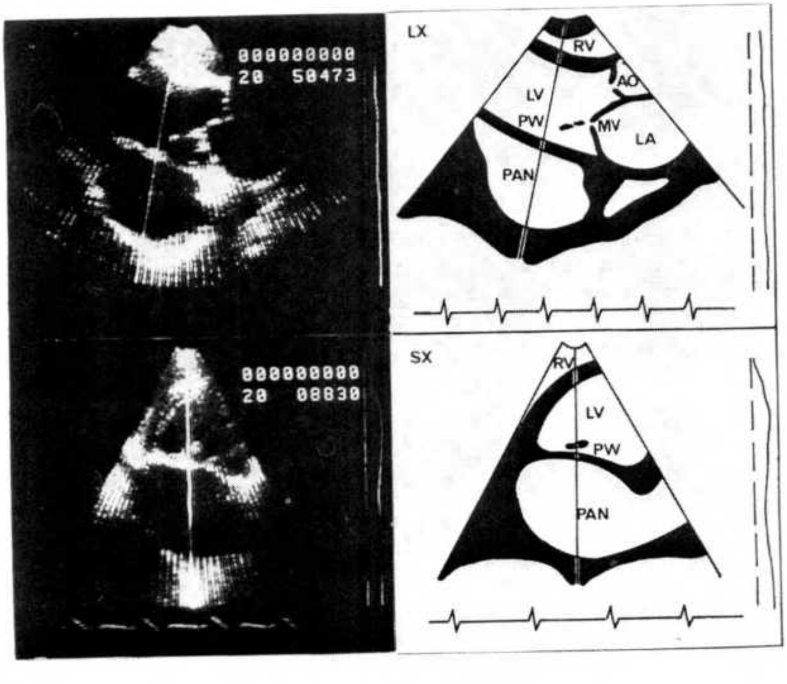

Fig. 2 *Original two-dimensional echocardiographic pictures in long axis (LX) and short axis (SX) on the left, with drawings on the right. In the long axis plane, aorta (AO), left atrium (LA), mitral valve (MV), and parts of the right (RV) and left (LV) ventricle are displayed simultaneously with the large saccular pseudoaneurysm (PAN) behind the posterior wall (PW) of the left ventricle.*

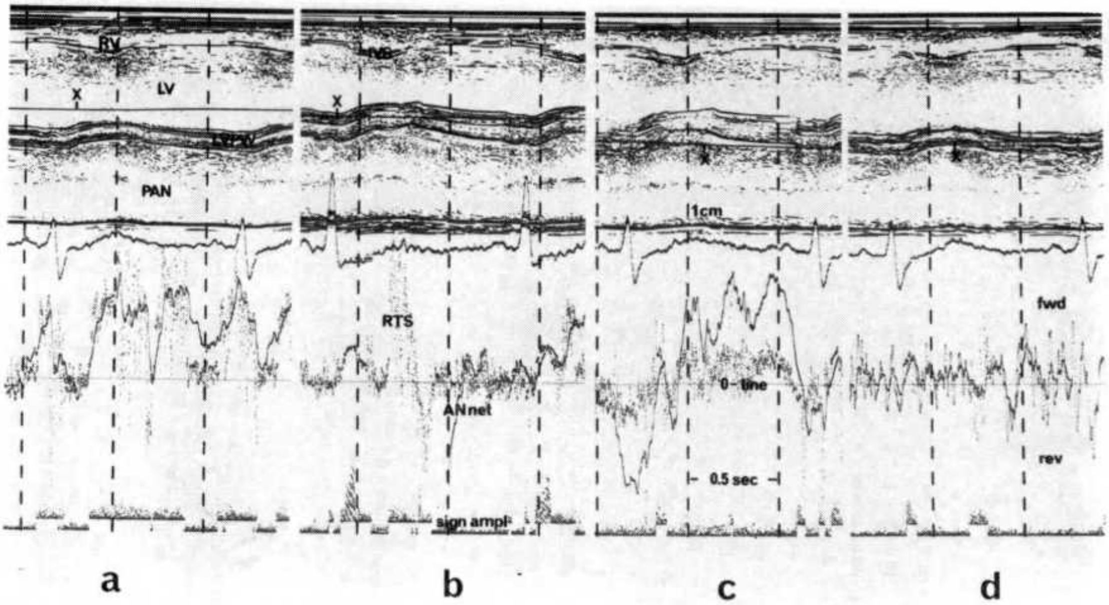

Fig. 3 *M-mode display with depth line, indicating the position of the sample volume* (upper half of the Fig.), *electrocardiogram in the middle part, Doppler-shifted frequency print-outs in real-time spectral (RTS), and analogue-net (ANnet) analysis* (lower half). (a) *Highly disturbed flow in systole and diastole with great turbulence in the apical portion of the left ventricle (LV).* (b) *A short systolic highly turbulent flow inside the left ventricular posterior wall (LVPW), marking the small communication defect.* (c) *The same disturbed flow pattern behind the posterior wall (LVPW) in the cavity of the pseudoaneurysm (PAN) as in the left ventricle (LV).* (d) *Only wall movement, no flow signals inside the normal left ventricular posterior wall (LVPW) M-mode abbreviations the same as in Fig. 1. Turbulent flow can be recognised best in the real-time spectral analysis print-out (RTS), while analogue-net curve (ANnet) shows more clearly the mean flow characteristics, that is the net-vector of forward (fwd) and reverse (rev) flow in every moment. O-line, zero-line of flow; sign ampl, signal amplitude, showing the strength of the flow signal going into the spectral processor.*

ECHOCARDIOGRAPHIC STUDY

These studies were performed with the Picker Echoview-80-C system interfaced with a Honeywell Visicorder 1856 and an 80° phased-array sector scanner Roche RT 400 using a hand-held 32-element double-frequency (2·25 and 3·5 MHz) transducer that electronically steers and focuses the ultrasound beam through the cardiac structures. A condensed M-mode scan (Fig. 1) begins with the demonstration of the aorta and the left atrium. As the sound beam passes deeper into the left ventricle a large echo-free extracardiac space can be recorded behind the posterior wall and the mitral valve area.

Two-dimensional echocardiographic studies were performed in the long axis and the short axis (Fig. 2). In the long axis image, aorta and aortic valve are displayed simultaneously with the mitral valve, the left atrium, the left ventricle, and the large saccular echo-free area behind the posterior wall.

In the short axis image the left ventricle is recorded just beneath the mitral valve. The shape of the left ventricle is grossly abnormal in that the posterior wall is fibrotic and flattened rather than circular. Motion of this area was an 'up-and-down' movement instead of a co-ordinated contraction. Behind the posterior wall the echo-free space is again seen, extending from the inferoposterior aspect to the lateral portion of the left ventricle.

PULSED DOPPLER ECHOCARDIOGRAPHIC STUDY

The pulsed Doppler echocardiographic study was performed with an ATL 500 A pulsed Doppler system previously described (Baker *et al.*, 1977), using a 3-MHz transducer focused at 7 cm and recorded with a Honeywell fibreoptic recorder LS-6AHS.

Fig. 3 and 4 show in the upper half the depth line within the M-mode display, indicating the position of the sample volume. In the lower half print-outs of the Doppler-shifted frequency spectrum (real-time spectral analysis, analogue-net curve, and signal-amplitude trace) are shown simultaneously with the electrocardiogram. In the apical portion of the left ventricular cavity a highly disturbed flow pattern with turbulence in systole and diastole is displayed (Fig. 3a).

Moving the sample volume into the posterior wall of the left ventricle (Fig. 3b), a short systolic, highly turbulent flow appears on the RTS print-out. This obviously marks the site of communication between the left ventricle and the pseudoaneurysm.

As the sample volume is advanced into the cavity of the pseudoaneurysm almost the same systolic-diastolic flow pattern as in the ventricular cavity is found (Fig. 3c). This indicates a free communication between both cavities. In Fig. 3d the sample volume is positioned in the normal left ventricular posterior wall where only some wall motion but no flow signals can be obtained. Fig. 4 shows a continuous frequency print-out as the sample volume is moved uninterruptedly from the cavity of the pseudoaneurysm (on the left) through the communication site of the posterior wall into the left ventricular cavity (on the right).

Blood flow signals can be shown again in both cavities and followed through the wall, thus marking the site of perforation and communication. In the posterior part of the false aneurysm no flow signals can be detected, indicating that the defect is very small, therefore not allowing propagation of left ventricular flow deeper into the cavity.

Discussion

Perforation of an infarcted area may result either in a spontaneous rupture with fatal outcome in the early stage of a myocardial infarction or in a slow progressive leakage of blood into the pericardial sac.

If there is partial adherence between pericardial and epicardial layers a local haematoma will be formed. This would be compatible with life (Gueron *et al.*, 1975). Diagnosis of pseudoaneurysms and their differentiation from true aneurysms is very important because of the tendency of false aneurysms to rupture even at a late stage (Vlodaver *et al.*, 1975). If diagnosed early enough surgery has proved successful (Davidson *et al.*, 1977).

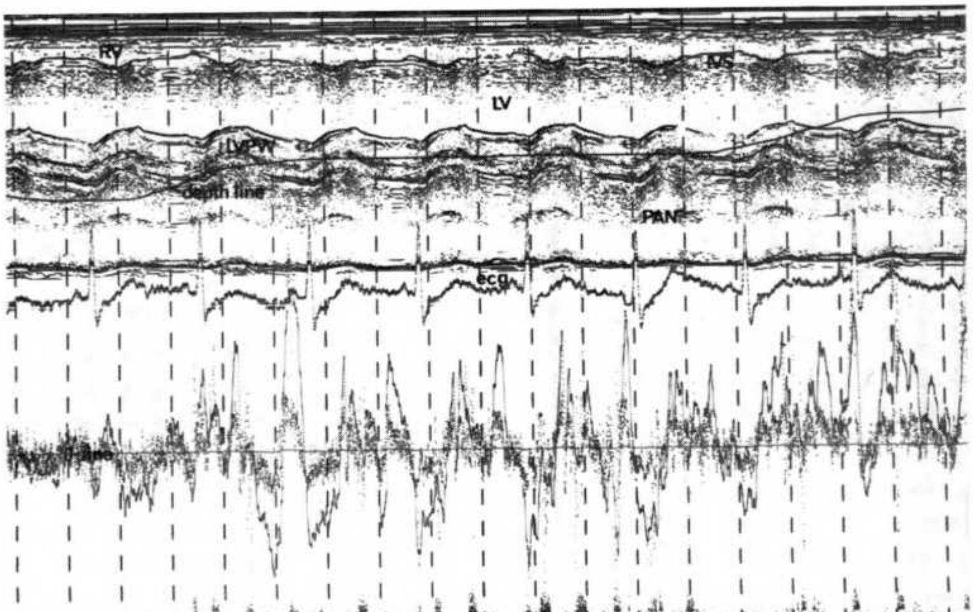

Fig. 4 *Frequency print-out of the continuous sample volume movement (depth line) from the anterior third of the cavity of the pseudoaneurysm (PAN)* (left) *to the direct vicinity of the left ventricular posterior wall (LVPW)* (middle), *and across it into the left ventricular cavity (LV)* (right). *No flow signals are found in the deeper part of the pseudoaneurysm; near the posterior wall there is systolic and diastolic flow movement that can be followed uninterruptedly across the wall into the left ventricle.*

It was concluded that the only possibility of differentiation between a false and a true aneurysm is the angiocardiographic visualisation of a small channel connecting the left ventricle with the cavity of the pseudoaneurysm. This, however, necessitates very careful cardiac catheterisation and the use of contrast medium.

As shown in this study and by others (Roelandt *et al.,* 1975; Davidson *et al.,* 1977), echocardiography is a very sensitive tool for demonstrating fluid-filled spaces behind the heart. This, and the unique ability of echocardiography to differentiate between soft tissue layers such as epicardium, pericardium, and myocardium and the ease of use make this non-invasive method very suitable.

Although M-mode echocardiography can detect and localise echo-free areas, two-dimensional echocardiography adds additional information because of the spatial orientation of the individual echoline in several examination planes. Thus size, shape, location, and extension of fluid-filled spaces and their respective walls can be shown with greater accuracy.

Despite these advantages, however, echocardiography is not reliable in differentiating between pseudoaneurysms, localised pericardial effusions, pericardial diverticula, large haematomas, or true aneurysms because beam width properties do not allow the demonstration of small-sized communication defects.

Definite diagnosis could only be made by angiocardiography. With the development of pulsed Doppler echocardiography a method is inaugurated that allows the determination of blood flow characteristics, that is turbulences or smoothness, exact timing, and direction of flow in any part of the cardiovascular system accessible to the investigation by ultrasound waves.

In this particular case it was possible to demonstrate similar blood flow patterns in the left ventricle and the cavity of the echo-free space in the direct vicinity of the left ventricular posterior wall, indicating that this space is in free communication with the ventricular cavity. Pericardial effusions, diverticula, or haematomas that have separating walls and no communication show no flow patterns within their cavities.

Differentiation between a false and a true aneurysm could be made by showing high systolic turbulence across the left ventricular posterior wall at the communication site and no flow movement in the middle and posterior part of the pseudoaneurysm.

This indicates a small restrictive defect that does not allow propagation of left ventricular pulsatile flow deeper into the cavity.

We conclude that pulsed Doppler echocardiography in combination with M-mode and two-dimensional echocardiography presents a safe and sensitive diagnostic method of detecting left ventricular aneurysms and in differentiating between false and true aneurysms.

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Br Heart J 1980; **43**: 237–240

Rheumatoid aortic valve prolapse requiring emergency aortic valve replacement

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SUMMARY Rapid progression of aortic regurgitation was closely observed in a patient with severe seropositive rheumatoid arthritis. Rheumatoid changes within the aortic valve leaflets resulted in severe prolapse necessitating emergency operation. The postoperative course was satisfactory.

Rheumatoid heart disease has been well recognised since Charcot's original description of rheumatoid pericarditis nearly 100 years ago (Charcot, 1881). Rheumatoid granulomata affecting the heart were first described in 1941 (Baggenstoss and Rosenberg, 1941) and since then many reports have appeared describing these specific lesions in all parts of the heart. Necropsy studies have shown an 11 per cent frequency of fibrinoid granulomata within the hearts of patients with rheumatoid arthritis (Barker, 1971), though this is probably an over-estimate arising from case selection. Aortic regurgitation is well recognised in this condition, though, if ankylosing spondylitis is excluded, it is rare, usually haemodynamically insignificant, and contributes little to the overall morbidity (Weintraub and Zvaifler, 1963). There are several reports of patients requiring aortic valve replacement, but in those cases in which there is adequate clinical and histological information the progression of the regurgitant valve lesion has with one exception been slow (Barker, 1971; Iveson *et al.*, 1975). These previous reports suggest that the regurgitation has been the result of either aortitis with dilatation of the aortic ring, or fibrosis, contraction, and destruction of the valve leaflets. We report a case of rapidly progressive aortic regurgitation caused by prolapse of leaflets softened and swollen by the rheumatoid process.

Case report

The patient was a white man born in 1912. At the age of 12 years he had an illness with arthralgia affecting many joints. There were no stigmata of carditis at that time. He was first seen at University College Hospital in 1969 when he presented with a classical history of angina pectoris. Good symptomatic relief was obtained with glyceryl trinitrate tablets. No abnormal signs were found on examination, and chest *x*-ray film and electrocardiogram were normal.

The following year he developed an arthritis predominantly affecting the hands and feet. A clinical diagnosis of rheumatoid arthritis was supported by the finding of high titres of rheumatoid factor in the blood. Since that time, relentless joint destruction has occurred despite the use of gold, penicillamine, and long-term steroid therapy, and he has also had recurrent episcleritis and a gastric ulcer. In April 1976, he had a transient episode of second degree heart block with Wenckebach phenomenon, and in September 1977 he had an episode of atrial flutter. It was thought that he might have a rheumatoid granuloma within the conducting tissue. In November 1977, he was admitted to another hospital with a flare-up of his arthritis and worsening angina. An episode of atrial fibrillation occurred but at all times the blood pressure was normal and there was no evidence of heart failure or myocardial infarction. On this admission an apical systolic murmur was heard for the first time. An echocardiogram performed in December 1977 was normal; in particular, there was no fluttering of the mitral valve.

In January 1978, he was admitted to University College Hospital with acute dyspnoea, and found to have severe rheumatoid changes in most peripheral joints and the cervical spine. The lumbar spine and sacroiliac joints were not involved. Rheumatoid nodules were present on both elbows. He was in sinus rhythm at 120 per minute with a normal pulse and a blood pressure of 140/90 mmHg.

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The apex beat was displaced 2 cm laterally but was not thrusting. There was an ejection systolic murmur and a soft early diastolic murmur at the left sternal edge. There were bilateral basal crepitations but no signs of right heart failure. A chest *x*-ray film showed a cardiac diameter of 16·5 cm and upper lobe vein blood diversion. The electrocardiogram was normal: there was no evidence of left ventricular hypertrophy or myocardial infarction. The serum levels of cardiac enzymes were not raised. The haemoglobin was 11·7 g/dl, white blood count $6{\cdot}2 \times 10^9$/1, and erythrocyte sedimentation rate 77 mm in the first hour. The response to a small dose of diuretic was dramatic. The aortic regurgitation was thought to be haemodynamically insignificant and his deterioration before admission was attributed to a transient arrhythmia. An echocardiogram showed a normal left ventricle, fluttering of the anterior cusp of the mitral valve, and a normal aortic valve and aortic root. During this admission he had minor exacerbations of arthritis associated with fever, malaise, and a rise in erythrocyte sedimentation rate to 120 mm in the first hour. There were no stigmata of bacterial endocarditis and repeated blood cultures were negative.

He was readmitted in pulmonary oedema on 11 March 1978. The signs of mild aortic regurgitation were unchanged with a blood pressure of 140/90 mmHg. The pulse was normal in character and the rhythm was sinus. There was no evidence of myocardial infarction. He again responded to diuretic therapy, though less quickly than before. His arthritis was still active, he was intermittently pyrexial, and he had an episode of episcleritis. On 22 March he developed a sinus tachycardia of 120 per minute with a collapsing pulse. The blood pressure fell to 100/30 mmHg. The murmur of aortic regurgitation was audible at the left sternal edge and there was also a mid-diastolic Austin Flint murmur at the apex. He developed severe left and then right sided heart failure which was resistant to medical treatment. Blood cultures, Coxiella antibody titre, fungal antibody tests, and ASO titre were all negative. An echocardiogram showed a slightly increased left atrial diameter of 4 cm, a left ventricular end-diastolic diameter of 5·5 cm, ejection fraction of approximately 70 per cent; the aortic valve and aortic root appeared normal, the fluttering mitral valve was seen to close prematurely, indicating severe aortic regurgitation of acute onset, and a pericardial effusion was also shown.

He was transferred to King's College Hospital for cardiac catheterisation and operation. The left ventriculogram was normal with an ejection fraction greater than 70 per cent. The aortogram confirmed the severe aortic regurgitation. Coronary angiograms showed a 90 per cent stenosis in the left anterior descending artery before the origin of its diagonal branch but no other stenoses.

At operation on 3 April 1978, 250 ml creamy fluid were found within a thickened pericardium. The aortic valve was tricuspid. There were no vegetations, and all three cusps were thickened and very soft. The left coronary cusp appeared to be prolapsing. There was no dilatation of the aortic ring. The aortic valve was replaced with a 25 mm Carpentier Edwards xenograft, and a saphenous vein graft was placed in the left anterior descending coronary artery.

The postoperative course has been satisfactory with all wounds healing well. He has had no further angina or signs or symptoms of heart failure and has returned home. He has had one further severe exacerbation of arthritis affecting the knees and ankles.

Histological examination of the thickened pericardium showed a chronic inflammatory infiltrate containing many plasma cells. Palisading was present along the surface as seen in a rheumatoid nodule. Sections of the aortic wall were normal. The thickening of the aortic valve cusps was the result of necrotic, partly calcified tissue lying between bands of connective tissue infiltrated by inflammatory cells (Fig. a, b). Palisading at the junction between normal valve tissue and the necrotic zone was poorly defined. The appearances were not pathognomonic of rheumatoid disease, but no other diagnosis was tenable.

Discussion

Necropsy studies have shown that there are two distinct histological types of rheumatoid heart disease: a non-specific inflammation with fibrosis, and a specific process (Bywaters, 1950; Sokoloff, 1953; Roberts *et al.*, 1968). The specific lesions are (a) the rheumatoid granulomata which are indistinguishable from the subcutaneous rheumatoid nodule and (b) a pathognomonic granulomatous and non-granulomatous inflammation occurring within a valve leaflet leaving a thin layer of uninvolved valve tissue necrotic material. This is clearly distinct from the valve lesion of rheumatic fever, carcinoid disease, or infective endocarditis (Roberts *et al.*, 1968). To make a firm diagnosis of rheumatoid heart disease, these specific histological features must be present. Our patient had both the classical rheumatoid involvement of both aortic valve and pericardium.

Operation became necessary in this patient within four months of the first appearance of an aortic regurgitant murmur, and 12 days after an

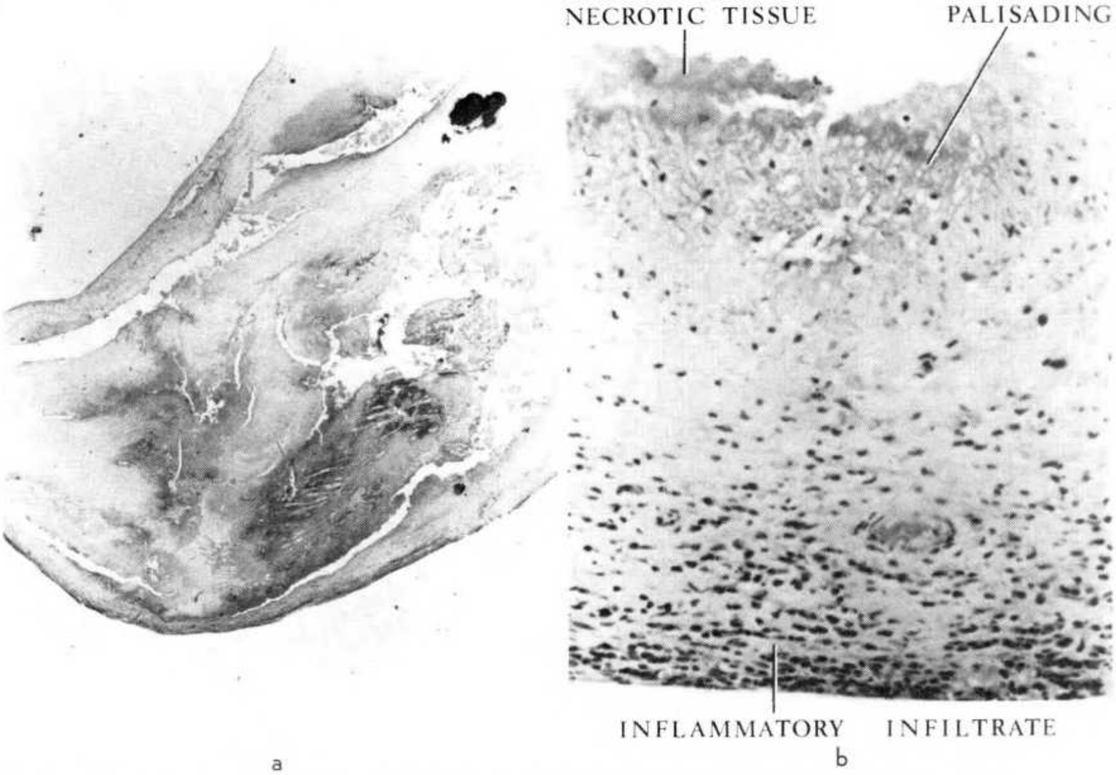

Fig. (a) *Low power section of aortic valve cusp showing inflamed valve tissue, enclosing amorphous, partly calcified necrotic tissue. (H and E. × 15 original magnification.)* (b) *High power view of one side of the aortic valve showing inflammatory infiltrate rich in plasma cells on the luminal surface and poorly defined palisading along the edge of the necrotic zone. (H and E. × 180 original magnification.)*

abrupt deterioration in his condition. Iveson *et al.* (1975) reported one patient who required aortic valve replacement within six months of the appearance of signs of aortic regurgitation, but in other well-documented cases the progression has been slow. At operation the valve leaflets were soft and swollen and the left coronary cusp of the aortic valve appeared to prolapse in the absence of aortic root dilatation. We believe that this prolapse of the softened leaflet accounted for the sudden deterioration of the patient's clinical condition. The clinical observations, the preoperative echocardiogram, and the left ventriculogram showing normal ejection fraction, suggest that myocardial failure was not responsible for the sudden decline. The successful postoperative course further supports this view. Had prolapse of the leaflet not occurred at this stage it is likely that the leaflets would have become fibrosed and contracted, as reported in all other cases.

The sudden deterioration had suggested the possibility of infective endocarditis with cusp rupture as an alternative to acute rheumatoid aortic valve disease; clinical features and laboratory investigations failed to distinguish between these alternative diagnoses.

We wish to emphasise that rheumatoid aortic valve disease may be haemodynamically significant and that it can be rapidly progressive simulating aortic cusp rupture. Features suggestive of rheumatoid valve involvement in this case and in other reports are the presence of subcutaneous nodules, episcleritis, and pericardial effusion (Bevans *et al.*, 1954; Weintraub and Zvaifler, 1963; Bonfiglio and Atwater, 1969; Iveson *et al.*, 1975).

We thank Dr Lyal Watson for permission to report this patient who was under his care.

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Br Heart J 1980; **43**: 241–243

Thrombosis and embolism complicating ventriculoatrial shunt for hydrocephalus: echocardiographic findings

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SUMMARY The echocardiographic findings of a right atrial thrombus and its migration to the right ventricle are presented. The thrombus occurred as a complication of an infected ventriculoatrial shunt system of the Pudenz-Heyer type for hydrocephalus.

The value of echocardiography in the diagnosis of atrial tumours and thrombi is well established (Effert and Domanig, 1959). We would like to document the echocardiographic findings of an unusual right atrial thrombosis and its embolisation in a 2-year-old child. The thrombus occurred as a complication of an infected ventriculoatrial shunt system of the Pudenz-Heyer type for hydrocephalus. It was first located in the right atrium, posterior to the tricuspid valve, then moved to the right ventricle, and finally led to embolic occlusion of the left main pulmonary artery.

Case report

In a female patient with sporadic achondroplasia abnormal head growth was observed at the age of 7 months. Cranial computer tomography, pneumoencephalography, ventriculography, and intraventricular pressure monitoring disclosed communicating, progressive hydrocephalus with considerably increased intraventricular pressure, exceeding the well-known moderate hydrocephalus in achondroplasia. Nine months after implantation of a Pudenz-Heyer type ventriculoatrial shunt, the child had several febrile episodes and was readmitted with severe *Staphylococcus aureus* septicaemia and ventriculitis.

CARDIAC FINDINGS AND COURSE

On admission a loud systolic murmur over the 3rd right intercostal space was found which was not present previously. Heart size was increased on *x*-ray examination, with infiltration of the right midlobe. Heart rate, blood pressure, and electrocardiogram were normal. Finally removal of the shunt, treatment of septicaemia, and digitalisation brought about some clinical improvement. One week later, however, sudden deterioration with paroxysmal ventricular premature beats (250/min) occurred. The systolic murmur changed considerably and became distinctly softer, and acute pulmonary thromboembolism was suspected. The patient died before surgery could be attempted.

ECHOCARDIOGRAPHIC FINDINGS

Echocardiograms were recorded from the fourth left intercostal space using a 5 MHz transducer and a Picker system. The first echocardiogram was recorded on admission, and showed a dense layer of finely structured echoes on the atrial side of the tricuspid valve (Fig. 1).

One week later, after the murmur had become softer, there was a significant change in the echo: in contrast to the first echo the right atrium was now absolutely free of echo, but the right ventricle into which the leaflets were opening, was filled out by dense, finely structured echoes which could also be recorded in the right ventricular outflow tract (Fig. 2).

POSTMORTEM FINDINGS

These included several small thrombi attached to the right atrium, to the chordae tendineae of the tricuspid valve, and to the right ventricle. One large thrombus completely blocked the left main pulmonary artery. Histological section showed no sign of old pulmonary thromboembolism or cellular reaction to the pulmonary thrombus.

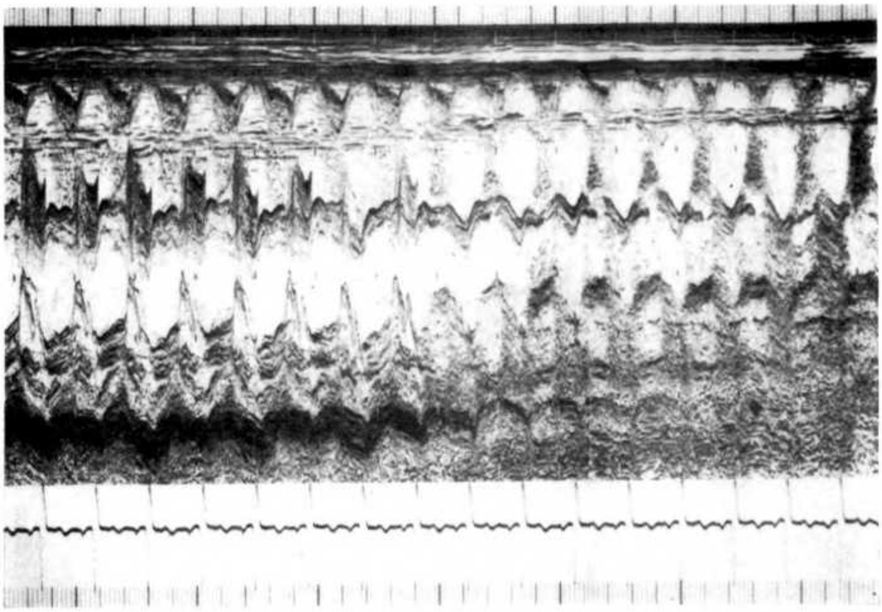

Fig. 1 *Echocardiogram on admission: the opening figure of the tricuspid valve is filled out by fine, dense echoes.*

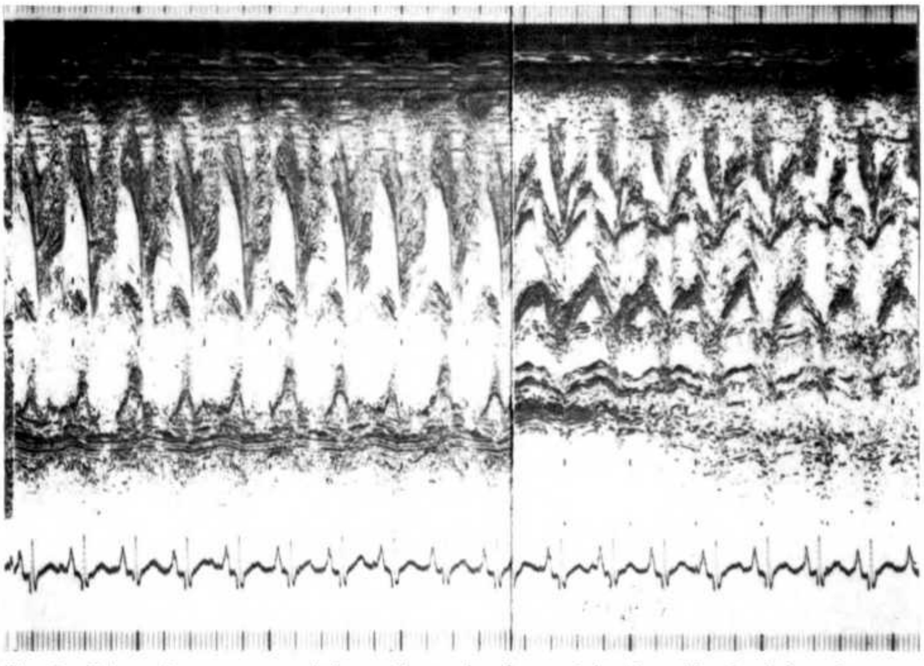

Fig. 2 *Echocardiogram one week later: the opening figure of the tricuspid valve is free of echoes which are now filling out the right ventricle (left), reaching into the outflow tract (right).*

Comment

Cardiopulmonary complications have been reported in 7 per cent of 143 patients treated with ventriculoatrial Pudenz-Heyer shunt for hydrocephalus (Anderson, 1973). Other complications included infections (29%) and blockage of the shunt (55%).

At necropsies of patients with ventriculoatrial shunts, cardiac and/or pulmonary thrombi were found in the vast majority of cases (Emery and Mahgrefte, 1969; Anderson, 1973). In many patients microembolisation is mild and intermittent, usually arising from the right atrium and so is difficult to recognise. But in some, it may lead to frank pulmonary hypertension and cor pulmonale (Keck *et al.*, 1978).

Previous shunt infections are found in most patients with thrombi (Jüngst *et al.*, 1977). Sudden death from embolisation of major thrombi is a permanent risk.

Echocardiography may be a useful means of early detection of major cardiac thrombi. In our patient we could follow the migration of the thrombus from the right atrium to the right ventricle by echocardiography. Though thrombectomy could not be performed in time in this particular patient because of concomitant severe infection, the story serves to emphasise that echocardiography should be included in the regular assessment of such patients, particularly when cardiopulmonary complications are suspected or infections of the shunt system occur.

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Br Heart J 1980; **43:** 244

Failure of prophylaxis for bacterial endocarditis: American Heart Association Registry

Sir,
The American Heart Association (AHA) recognises that its current recommendations for antibiotic prophylaxis are necessarily empirical[1] because important clinical information on the efficacy of antibiotic prophylaxis of bacterial endocarditis is lacking. The present recommendations are therefore based upon secondary sources of information such as the relative propensity of various procedures to cause bacteraemia, in vitro studies of bacteria recovered from the blood, the effect of antibiotics on bacteraemias, the susceptibility of various heart lesions to infection, anecdotal case reports, and study of experimental models.

Although over 30 individual cases of apparent failure of prophylaxis have been recorded, many of our colleagues have rightly pointed out that the evidence indicating that a significant number of failures actually occurs is inconclusive. This question is of considerable medical and medicolegal importance because of the frequent necessities for measures to prevent endocarditis, and because of the serious consequences of failure to prevent the disease.

In an attempt to accumulate useful epidemiological data, the AHA Committee has established a Registry to record cases of apparent failure of antibiotic prophylaxis of bacterial endocarditis. We are now soliciting case reports. Notification may be made on a simple preprinted postcard, which will require only identification of the patient and the name, address, and telephone number of the person referring the case. These postcards will be made available to doctors and dentists and to any other person or organisation requesting them from the AHA or from one of us. Alternatively, a case may be reported directly to one of us, at the address or telephone number listed below. After notification, one of us will follow up with a telephone call, in order to gather sufficient information to evaluate the case. All such information will be confidential.

Though there are obvious disadvantages to any retrospective evaluation such as this, the practical impossibility of conducting a prospective trial of different modes of prophylaxis has caused us to seek alternative means of gathering data. We hope that a useful body of information may be accumulated, which may influence future recommendations for prophylaxis of endocarditis.

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[1] American Heart Association Committee on Rheumatic Fever and Bacterial Endocarditis. Prevention of bacterial endocarditis. *Circulation* 1977; **56:** 139A-43A.

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(1) *Standard journal article*—(List all authors when six or less; when seven or more, list only first three and add *et al.*):
Walmsley R. Anatomy of left ventricular outflow tract. *Br Heart J* 1979; **41:** 263–67.

(2) *Books and other monographs:*
Macartney FJ, Partridge JB, Shinebourne EA, Tynan MJ, Anderson RH. Identification of atrial situs. In: Anderson RH, Shinebourne EA, eds. *Paediatric cardiology* 1977. Edinburgh, London: Churchill Livingstone, 1978: 16–26.

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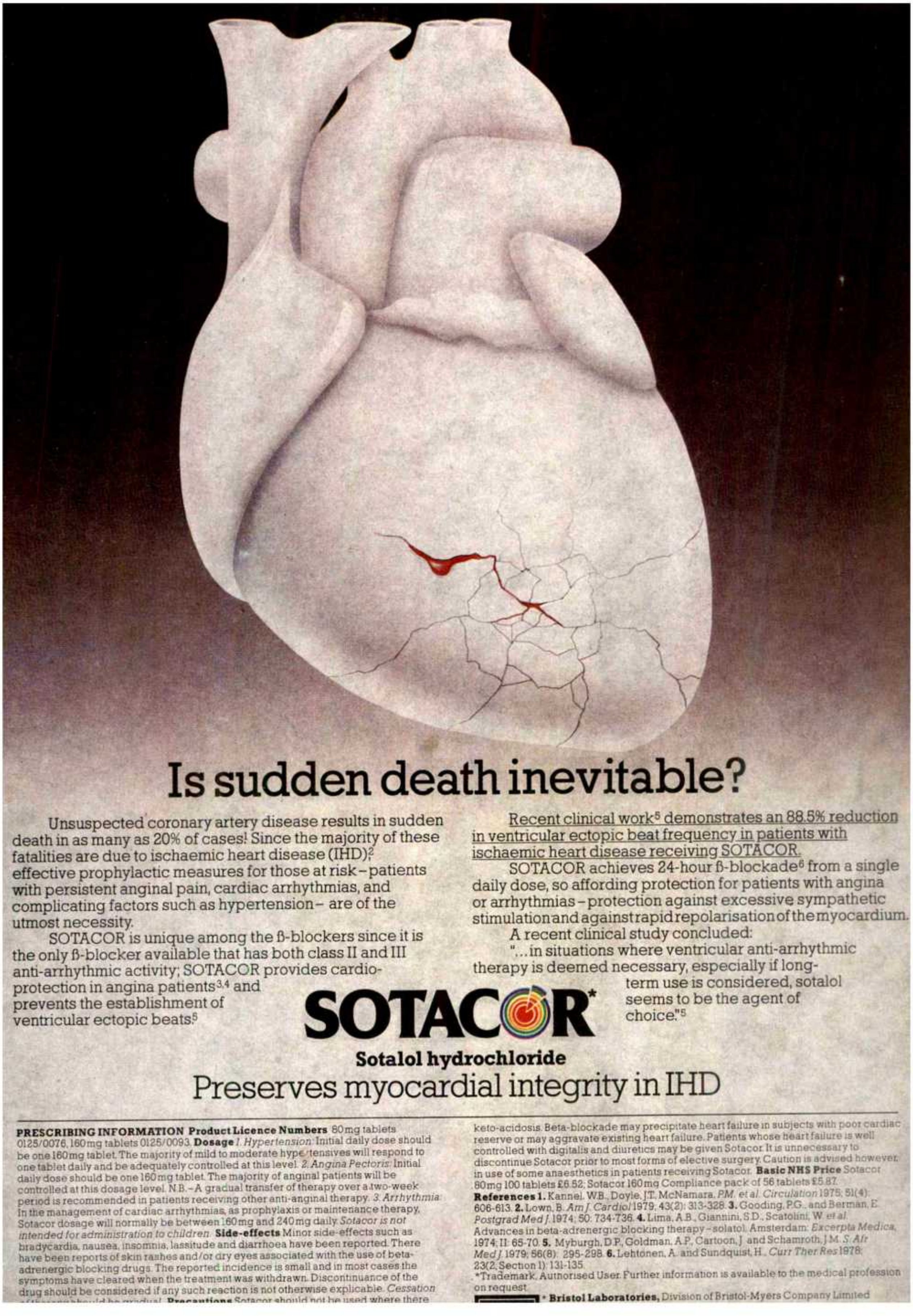

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Unsuspected coronary artery disease results in sudden death in as many as 20% of cases.[1] Since the majority of these fatalities are due to ischaemic heart disease (IHD)[2] effective prophylactic measures for those at risk – patients with persistent anginal pain, cardiac arrhythmias, and complicating factors such as hypertension – are of the utmost necessity.

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References **1.** Kannel, W.B., Doyle, J.T., McNamara, P.M. et al. *Circulation* 1975; 51(4): 606-613. **2.** Lown, B. *Am J Cardiol* 1979; 43(2): 313-328. **3.** Gooding, P.G., and Berman, E. *Postgrad Med J.* 1974; 50: 734-736. **4.** Lima, A.B., Giannini, S.D., Scatolini, W. *et al.* Advances in beta-adrenergic blocking therapy – solatol. Amsterdam: *Excerpta Medica,* 1974; II: 65-70. **5.** Myburgh, D.P., Goldman, A.P., Cartoon, J. and Schamroth, J.M. *S Afr Med J.* 1979; 56(8): 295-298. **6.** Lehtonen, A. and Sundquist, H., *Curr Ther Res* 1978; 23(2, Section 1): 131-135.

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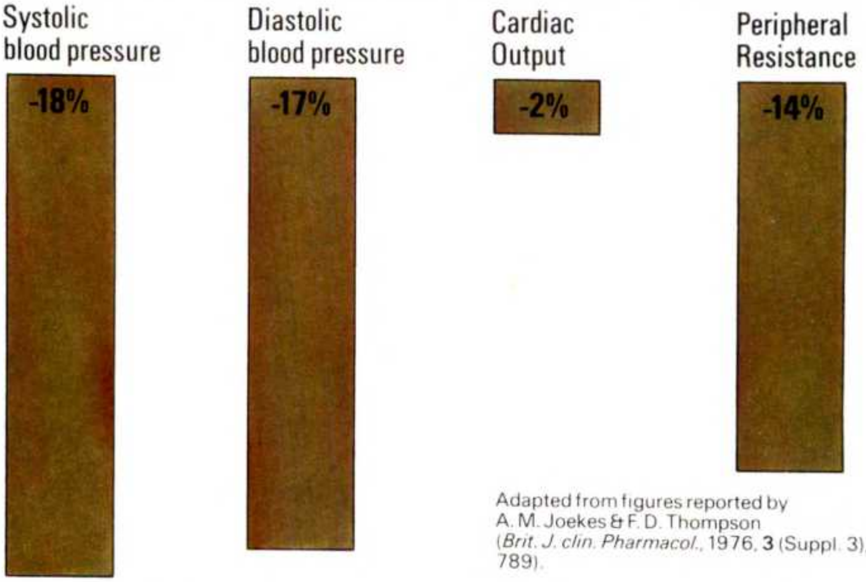

Adapted from figures reported by A. M. Joekes & F. D. Thompson (*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

The above figure shows the mean haemodynamic changes in 14 hypertensive patients given intravenous Trandate 0.5-1.0mg/kg

In essential hypertension the usual haemodynamic changes are increased blood pressure and peripheral resistance while cardiac output remains normal.

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Subsequent treatment can be continued with the same drug given orally

"A practical advantage associated with labetalol is that oral treatment can be instituted immediately after using the intravenous form."

(Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

"There are many advantages to using a compound that can be given intravenously to control blood pressure in patients with small vessel disease or impaired renal function, which is then available for long-term oral therapy."

(Joekes, A. M. & Thompson, F. D., *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789–793)

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(Morgan, T. et al, *Med. J. Australia*, 1978, **i**, 393)

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(Altman, M., *J. Pharmacotherapy*, 1978, **1**, 208)

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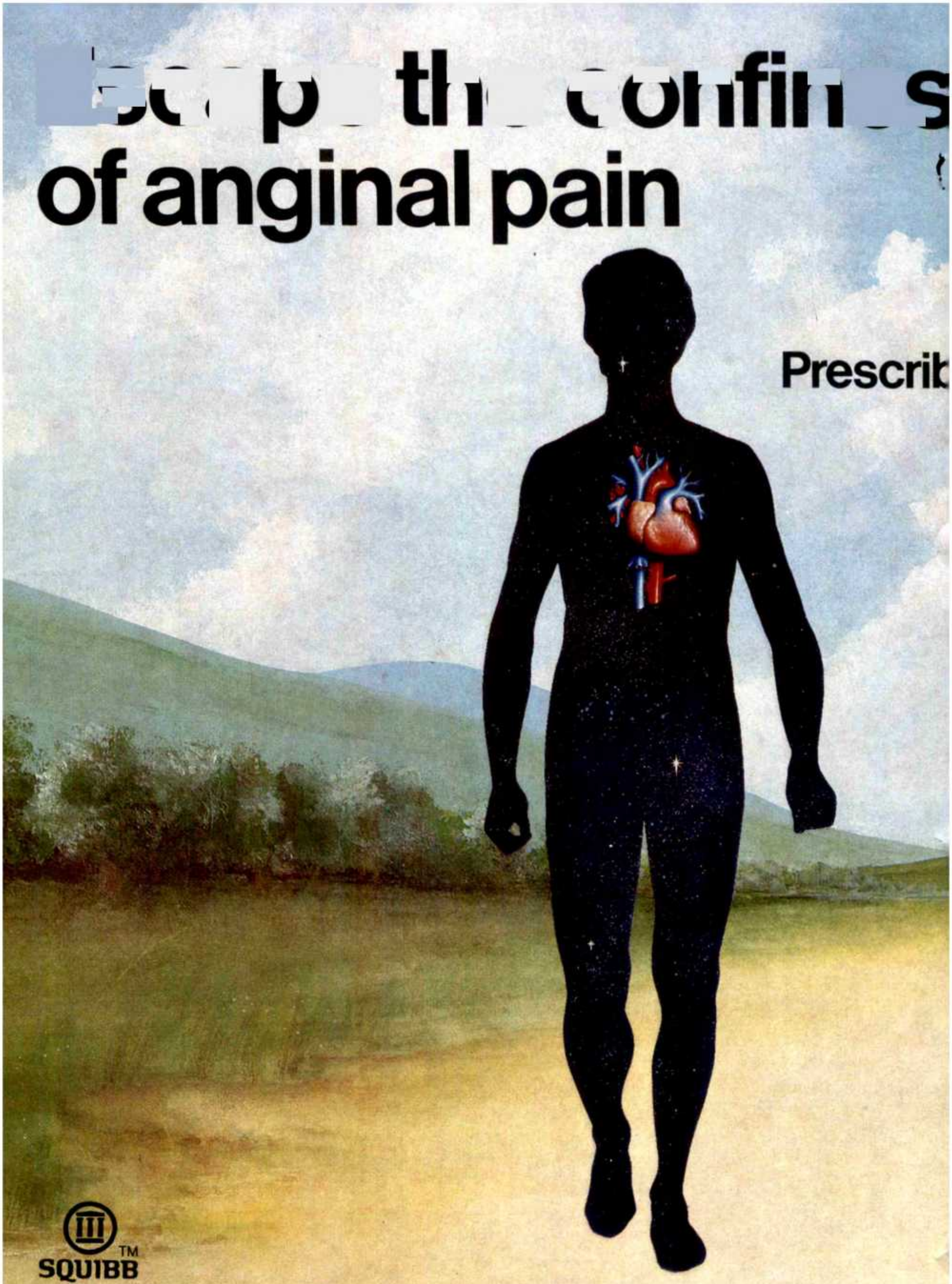

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Nadolol may be given in a once daily dosage without regard to meals.
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The value and safety of daily doses exceeding 240 mg have not been established.
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Contra-indications
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Warnings
The normal precautions associated with the use of beta-adrenergic blockers should be followed.
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Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus.
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The safety of nadolol in pregnancy has not yet been established, and nursing mothers should only receive nadolol if deemed essential.

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Product Licence Numbers
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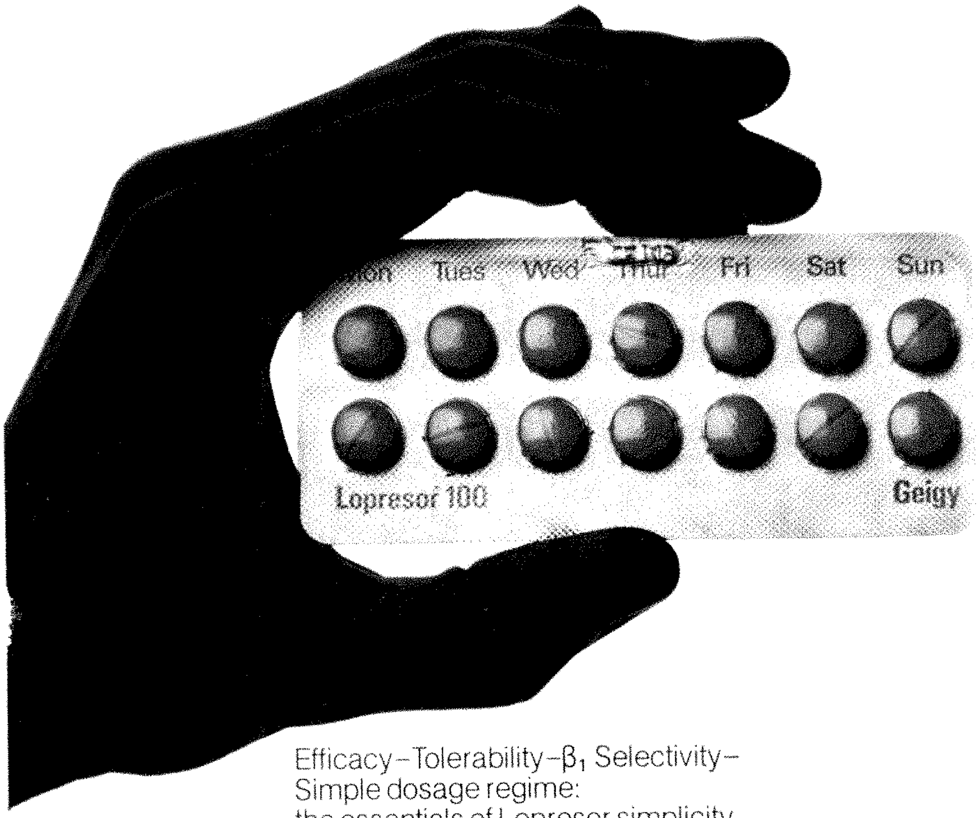

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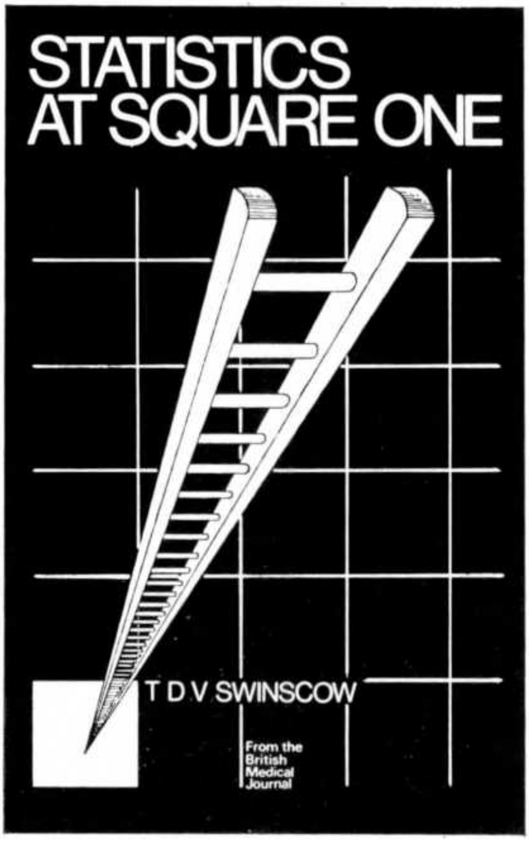

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Br Heart J 1980; **43**: 245–251

Sudden death in hypertrophic cardiomyopathy: associated accessory atrioventricular pathways*

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JOHN F GOODWIN, ROGER C EVANS, DAVID B SHAW

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SUMMARY Sudden death is a known but unpredictable complication of hypertrophic cardiomyopathy. We describe two patients who both had a strong family history of the disorder complicated by sudden death. Necropsy disclosed accessory bypass tracts, concealed in one and previously suspected in the other. One died from ventricular fibrillation and the other, who died outside hospital, had previously complained of palpitation. Arrhythmia complicating pre-excitation appears to be one of the factors responsible for sudden death in hypertrophic cardiomyopathy.

Arrhythmias may be responsible for some cases of sudden death, the most unpredictable and devastating result of hypertrophic cardiomyopathy, and it has been postulated that a proportion of these might occur on the basis of accessory atrioventricular pathways.[1] Though we demonstrated that concealed pre-excitation[2] in hypertrophic cardiomyopathy could cause re-entrant atrioventricular tachycardia,[1] we had no evidence that abnormal atrial activity could reach the ventricles prematurely and initiate ventricular fibrillation, as in some cases of the Wolff-Parkinson-White syndrome.[3] We now report two patients with hypertrophic cardiomyopathy who died suddenly: they showed identical pathological features, with unusual accessory pathways.

Case reports

CASE 1

A 17-year-old Yugoslav girl first experienced syncope after exercise at the age of 9. Subsequently mild exercise produced dyspnoea, light-headedness, exhaustion, and palpitation. There had been six episodes of syncope without chest pain and several attacks suggestive of paroxysmal tachycardia. In July 1976 cardiac catheterisation and angiocardiography in Yugoslavia showed mitral regurgitation and hypertrophy of both ventricles especially obvious in the interventricular septum, but no intraventricular gradient (details of pressures, and films, are not available). Both her brothers had died suddenly, one at the age of 5 and the other at the age of 15.

Examination disclosed left ventricular hypertrophy with a palpable atrial beat and a systolic murmur; blood pressure 110/70 mmHg. The electrocardiogram (Fig. 1) showed sinus rhythm, disturbed atrial depolarisation, first-degree atrioventricular block, moderate left ventricular hypertrophy, and impairment of intraventricular conduction. Chest *x*-ray film showed no evidence of raised left atrial pressure but there was left atrial and ventricular enlargement.

During an intracardiac electrophysiological study[4] the AH and HV intervals were normal at 80 and 45 ms during sinus rhythm and at the start of atrial pacing (Fig. 2). Incremental right atrial pacing showed 1:1 atrioventricular conduction via the atrioventricular node up to a rate of 187 a minute (Fig. 3) during which the AH interval did not lengthen but the HV prolonged slightly (60 ms). The intraventricular conduction pattern remained unchanged until complex 12; impulses 13 and 14 showed earlier and wider QRS complexes and shorter HV times (40 ms), that is earlier ventricular activation. The next stimulus failed to depolarise the ventricles because of atrioventricular block; in complex 15 the HV interval and QRS pattern were as in 1 to 12, but from 19 onwards the QRS

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*The studies at the Royal Postgraduate Medical School were supported in part by the British Heart Foundation.

Received for publication 12 September 1979

complexes were again wide and HV shortened. Stimulation was stopped immediately after complex 26 by which time the patient was in ventricular tachycardia which degenerated into ventricular fibrillation. Though she was promptly defibrillated she was unable to achieve any cardiac output in sinus rhythm or with pacing.

At necropsy, the total heart weight was 510 g, with gross biventricular hypertrophy (Fig. 4). The interventricular septum was asymmetric in relation to the posterior wall of the left ventricle, measuring 2·9 cm against 1·5 cm (ratio 1·9:1). The septum bulged into both right and left ventricular outflow tracts. The left ventricular cavity was small (2·1 cm in diameter at mid-ventricular level). A band of endocardial fibrous tissue was present on the left side of the interventricular septum forming a mirror image to the anterior cusp of the mitral valve; this finding suggests contact between the septum and anterior cusp during life. On histological examination the myocardium showed the typical malarrangement of hypertrophic cardiomyopathy throughout the whole septum, extending into the free walls of both ventricles. Only in a small lateral segment of the right ventricle and a posterolateral segment of the left ventricle were the muscle fibres normally arranged.

The conduction system and both atrioventricular rings were studied by serial histological section at 120 μ intervals. The sinus node, atrioventricular

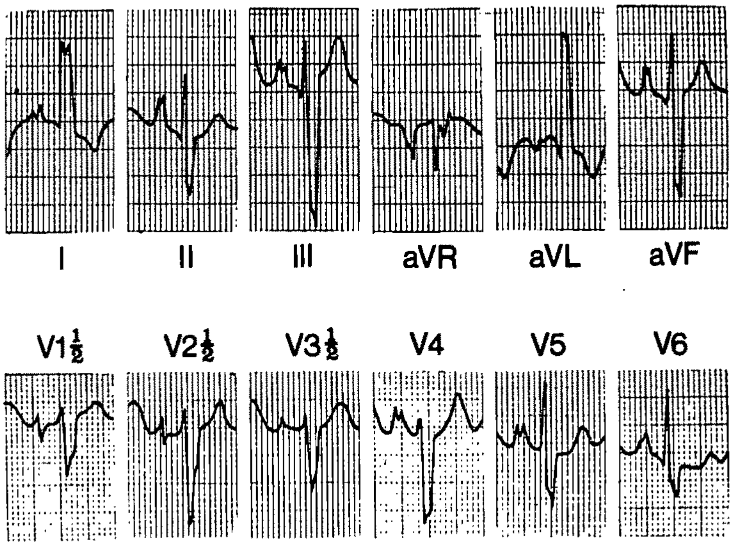


Fig. 1 *Electrocardiogram of case 1. Note the presence of distorted P waves, slight PR prolongation, mild left axis deviation, poor R wave development in right praecordial leads, broad S waves in left praecordial leads, and ST depression and/or T wave inversion in leads I, aVL, and V5–6.*

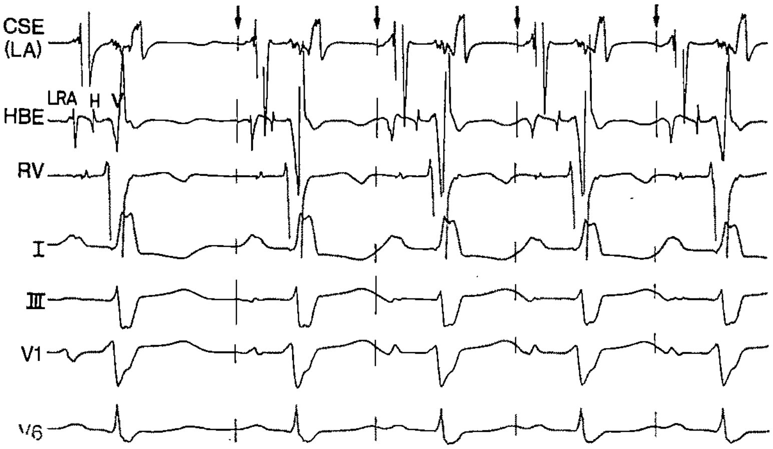


Fig. 2 *Simultaneous intracardiac and surface electrocardiographic recordings in case 1. The arrows, and corresponding artefacts, indicate right atrial stimulation. In addition to leads I, III, V1, and V6, tracings were recorded from the coronary sinus (CSE), reflecting activity from the left atrium (LA); the low right atrium and ventricle (HBE, His bundle electrogram); and right ventricle (RV). LRA, low right atrial depolarisation; H, activation of bundle of His; V, ventricular activation. Paper speed 100 mm/s.*

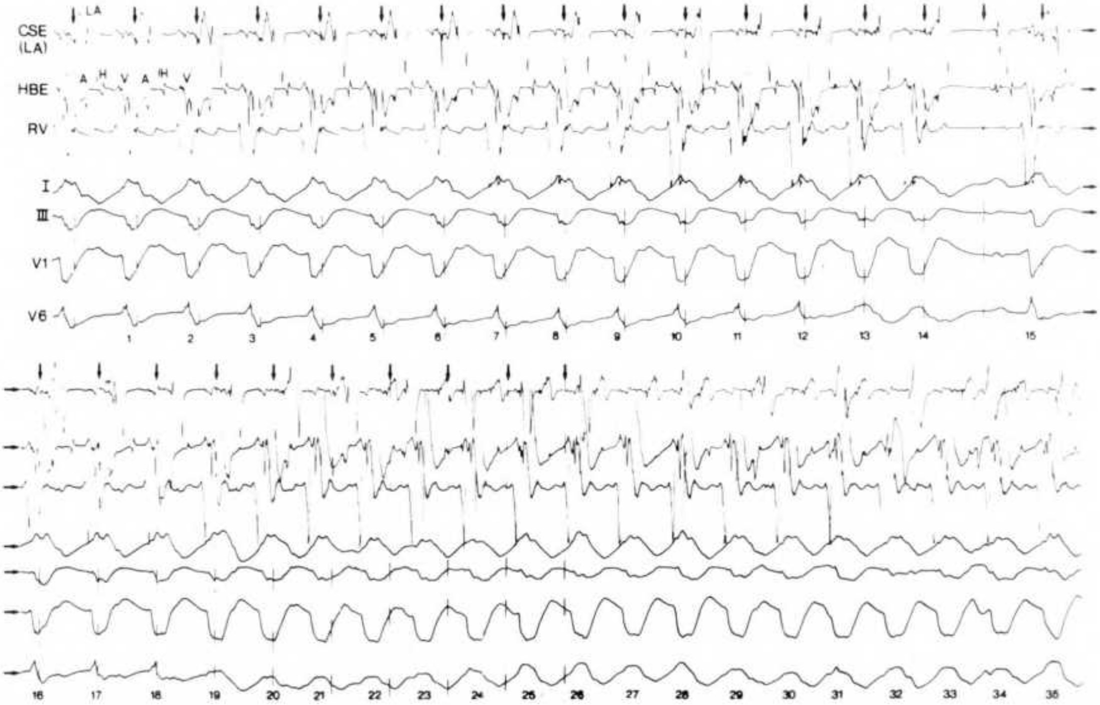


Fig. 3 *Recordings as in Fig. 2, with incremental right atrial pacing. Each stimulus is followed by ventricular activation with consistent QRS morphology until complexes 13 and 14, when QRS is broader and ventricular activation earlier; 2:1 atrioventricular block follows complex 14, complexes 15 to 18 resembling earlier patterns. From 19 onwards, QRS is widened and ventricular depolarisation earlier; after 26 there is independent ventricular tachycardia.*

node, penetrating and bifurcating main bundle, and proximal bundle-branches were within normal morphological limits. On the right side of the interventricular septum, muscle bands passed up under the septal cusp of the tricuspid valve and, because of fragmentation of the collagen of the central fibrous body, made multiple connections with atrial muscle fibres running immediately beneath the right atrial endocardium superficial to the atrioventricular node (Fig. 5). These atrioventricular connections occurred in an area 0·5 cm in length and were composed at the ventricular end of hypertrophic disorganised muscle which extended anteriorly close to the right bundle-branch.

CASE 2

A 28-year-old woman had been found at the age of 5 to have a systolic murmur which was initially attributed to a ventricular septal defect. The electrocardiogram then was said to show left bundle-branch block; later the PR interval was seen to be short and Wolff-Parkinson-White syndrome was suspected. She had no cardiac symptoms until the

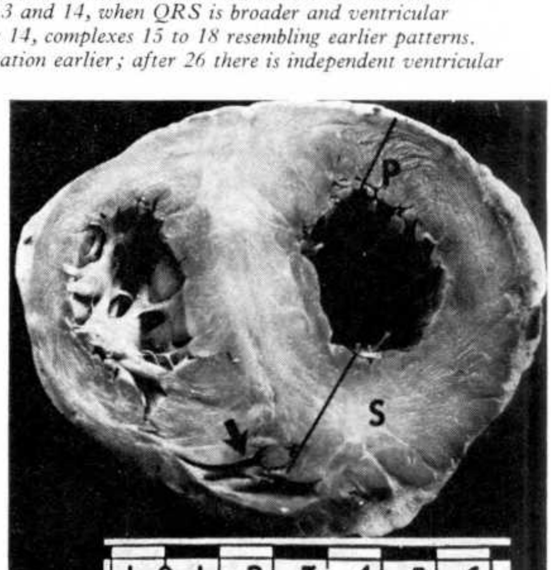
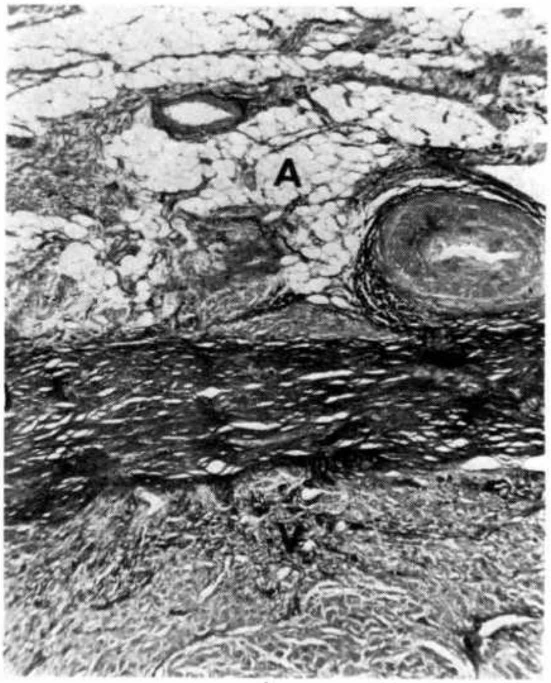


Fig. 4 *Transverse section of left and right ventricles of case 1. The anterior portion of the interventricular septum (S) is disproportionately thickened in comparison with the posterior left ventricular wall (P). The septum bulges into the right ventricular outflow tract* (arrow).

menarche (age 13) when she developed palpitation, aggravated by effort, before each period. At the age of 18 the cardiac apex was normal, there was an early aortic systolic murmur, grade 3/6; blood pressure 160/80 mmHg, and electrocardiogram unchanged (Fig. 6a). Practolol 100 mg twice daily had little effect but propranolol appeared to reduce the number of attacks. Dyspnoea on effort first developed at the age of 24. The electrocardiogram now showed even greater PR shortening, and wider QRS complexes with increased voltage and smaller

Fig. 5 *Histological sections of heart (case 1).* (a) *The plane of section passes through the atrial and ventricular septum immediately posterior to the atrioventricular node. Adjacent to the mitral valve (M), atrial (A) and ventricular (V) muscle are clearly separated by the fibrous body. Adjacent to the tricuspid valve (T) a mass of muscle* (arrows) *from the ventricular septum pushes up under the septal cusp and the fibrous body is indistinct. (Van Gieson. Original magnification ×14.)* (b) *Area adjacent to the mitral valve in* (a). *Atrial muscle (A) is separated from ventricular muscle (V) by a distinct mass of fibrous tissue. (Van Gieson. ×100.)* (c) *Area adjacent to the tricuspid valve in* (a). *Multiple strands of muscle* (arrow) *pass from atrial (A) to ventricular (V) muscle; no defined fibrous body is present. (Haematoxylin and eosin. ×100.)*



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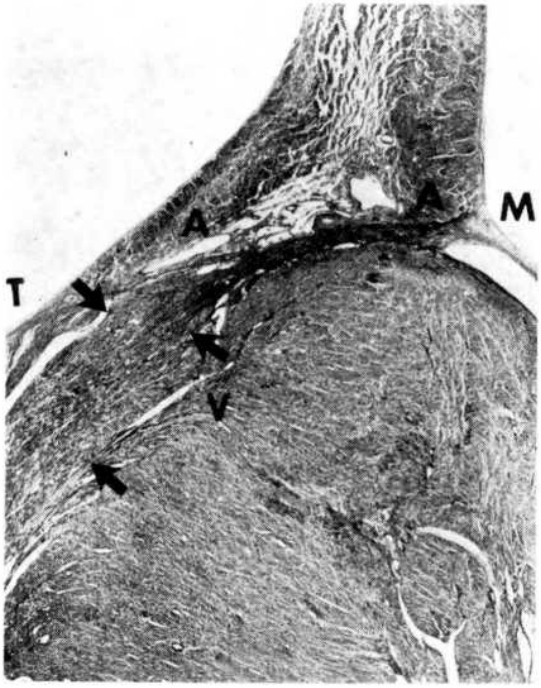

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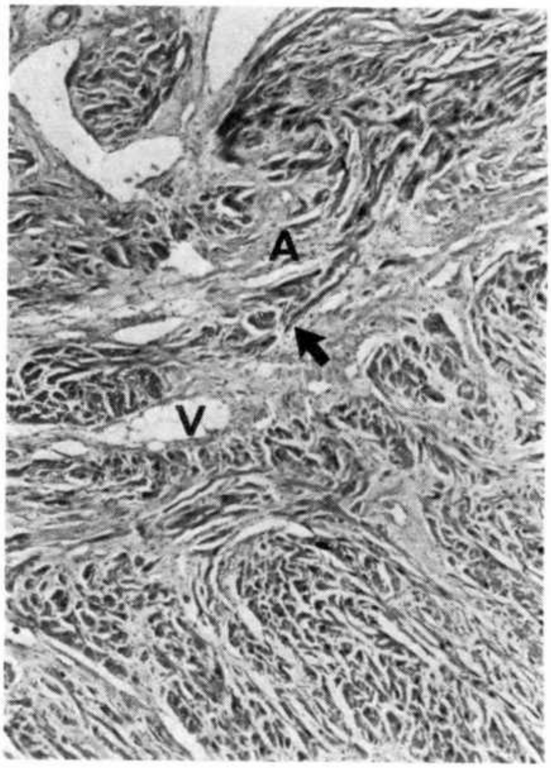

c

R waves in right praecordial leads (Fig. 6b). Electrophysiological investigations were considered but deferred; three months later she collapsed while clearing away snow and was dead on arrival at hospital.

Her father had died suddenly at the age of 31, necropsy showing pronounced hypertrophy of both ventricles, the left more than the right (heart weight 575 g). A younger sister died suddenly at the age of 9: the heart weighed 300 g and there was 'moderate degree of generalised hypertrophy' without outflow tract obstruction. Her only brother is 27, alive, symptom-free, and without clinical or electrocardiographic abnormality.

At necropsy, the total heart weight was 560 g, with biventricular hypertrophy. The interventricular septum measured 4 cm and the posterior left ventricular wall 2·2 cm (ratio 1·8:1). The left ventricular cavity was small (2 cm at mid-ventricular level). Abnormally arranged muscle was present in the majority of both ventricles, only sparing a small posterior segment of each. Involvement of the right ventricular free wall in the outflow produced anatomical obstruction.

The conduction system and the whole of both atrioventricular rings were examined by serial section. The atrioventricular node, main bundle, and proximal bundle-branches were normal. The left bundle-branch in the mid-septal zone showed some attenuation and stretching with distinct endocardial fibrosis. In the right atrioventricular groove, anteriorly over an area of 3 mm, a band of subepicardial atrial fibres made connection with a mass of ventricular fibres (Fig. 7) that showed the typical arrangement of hypertrophic cardiomyopathy. A second small atrioventricular connection was present in the interventricular septum in the identical position to that of case 1. This connection, consisting of a single muscle bundle 20 μ across, joined abnormal muscle in the interventricular septum to the atrial fibres passing down superficial to the atrioventricular node.

Discussion

Both patients were young women who had symptoms and a strong family history of sudden death. In the first patient ventricular fibrillation followed atrial stimulation during an electrophysiological study; the other had previously been shown to have electrocardiographic abnormalities consistent with pre-excitation. The electrophysiological study was performed in the first patient to see whether means could be found to prevent sudden death, the major hazard to which she was liable. At necropsy both patients were found to have hypertrophic cardiomyopathy and identical and unusual accessory atrioventricular connections made up of the same type of tissue as was found in the ventricles. Though mechanisms other than arrhythmias undoubtedly produce sudden death in some patients,[1] and other arrhythmias, for example ventricular tachycardia, may occur,[5 6] our hypothesis has been substantiated as far as these two patients are concerned.[1] Further investigation is required to see how common this phenomenon is and whether one can prevent this outcome.

The possibility that, in case 1, there was enhanced atrioventricular conduction through the node seems to us a much less reasonable explanation in the face of the anatomical abnormality, and because the alteration in QRS morphology is consistent with stimulation of the right ventricle through an accessory pathway in that particular location. This

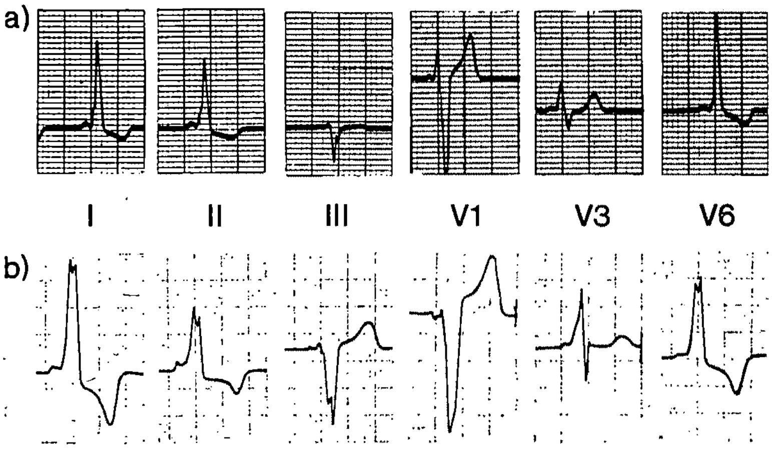

Fig. 6 *Electrocardiograms of case 2* (a) *in early childhood and* (b) *three months before death. In both there are short PR intervals and wide QRS complexes, but the latter tracings show greater widening and distortion of the QRS complexes and more obvious ST-T depression and inversion, with loss of the R wave in V1. In both instances, the upstroke of R is slurred, resembling a delta wave.*

is supported by the fact that, after resumption of atrioventricular conduction at complex 15, the QRS morphology reverted to its previous appearance; the early ventricular activation is of crucial importance and, we believe, most consistent with the anatomical findings.

Patients with hypertrophic cardiomyopathy who die suddenly are often children and young adults, and there may be a relation to physical exertion; in addition there are electrocardiographic abnormalities including increasing left ventricular hypertrophy and pronounced ventricular septal thickening.[7] This may occur in families who may show an unusually severe expression of the disorder.[8] Abnormal accessory atrioventricular communications were not reported in these cases,[7] though septal clefts have been considered to be responsible.[9] We did not think that such changes could explain the electrophysiological abnormalities found in patients suffering from re-entrant atrioventricular tachycardia caused by concealed pre-excitation in hypertrophic cardiomyopathy,[1] and had proposed to investigate the electrophysiological characteristics of patients at risk of sudden death with a view to finding factors that might prevent this.

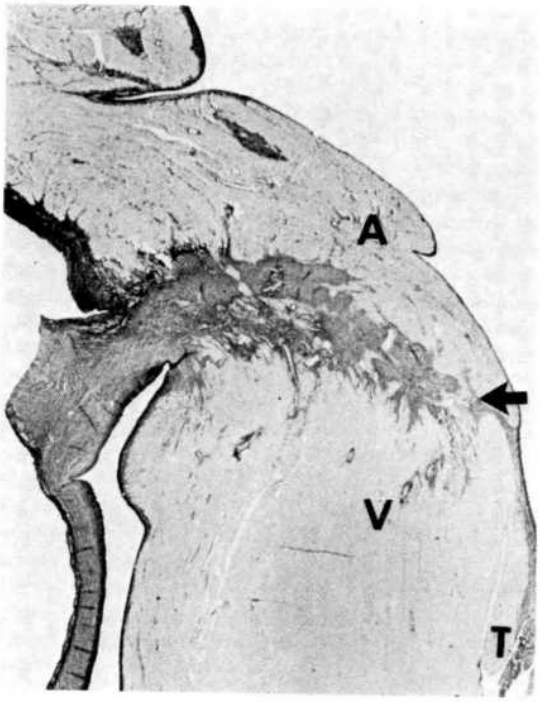

Fig. 7 *Section through the heart of case 2, passing through atrial (A) and ventricular (V) septa immediately posterior to the atrioventricular node. The central fibrous body is penetrated by a mass of muscle* (arrow) *extending under the tricuspid valve (T) and connecting atrial and ventricular septa. (Van Gieson. ×10.)*

Though it has been suggested that pre-excitation and hypertrophic cardiomyopathy frequently coexist, a review of published cases showed that this association was infrequent[10]; we felt that in many the appearances were the result of a combination of shortening of the PR interval and abnormal intraventricular conduction as well as hypertrophy.[1] Careful electrophysiological study of 13 patients with proven hypertrophic cardiomyopathy showed a high incidence of arrhythmias and conduction abnormalities, particularly within the His-Purkinje system,[11] though we think it will be necessary to show whether similar findings might occur in patients with left ventricular hypertrophy of similar degree but resulting from other causes. In none of the 13 cases were there signs of pre-excitation though atrioventricular nodal behaviour suggested a possible tendency for the development of intranodal reciprocating tachycardias.[11]

We have not carried out further invasive electrophysiological investigations on patients with high-risk cardiomyopathy as judged by the family history and findings thought to suggest the likelihood of sudden death.[6 12] As patients with this disease are notoriously difficult to resuscitate from ventricular fibrillation, doubtless because of the grossly diseased myocardium, such studies should probably be avoided in high-risk patients at this stage of our knowledge.

The electrocardiogram in the first patient showed no evidence of pre-excitation while that in the second did suggest the Wolff-Parkinson-White syndrome, though probably, at least latterly, modified by left bundle-branch block.[13] The location of the bypass in the first case is consistent with the electrophysiological findings; when right atrial stimuli blocked the atrioventricular node and engaged the bypass, the QRS complexes were premature and resembled left bundle-branch block because the earliest part of the ventricles to be excited was the right upper interventricular septum. Pre-excitation was also shown by unduly rapid transmission of atrial impulses to the ventricles[14] and HV shortening,[4] both of which reflect the absence of normal atrioventricular nodal delaying properties. In the second case there were two bypasses; it is impossible, without electrophysiological study, to know which was implicated.[10] It is more likely that the abnormal tissue found in hypertrophic cardiomyopathy invaded pre-existing latent accessory pathways[2] rather than eroding the annulus fibrosus or central fibrous body.

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Br Heart J 1980; **43**: 252–261

Exercise testing after beta-blockade: improved specificity and predictive value in detecting coronary heart disease

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SUMMARY The value of exercise testing in detecting myocardial ischaemia resulting from coronary atheroma remains controversial. In order to increase the reliability of exercise testing, all its components (symptomatic, haemodynamic, and electrocardiographic) have been scrutinised. In this study, concerned only with the electrocardiographic response to exercise, the incorporation of beta-blockade into the standard exercise procedure has improved specificity and predictive value without affecting sensitivity.

Fifty patients with anginal pain and 50 asymptomatic subjects with an abnormal electrocardiogram were investigated by exercise testing before and after beta-blockade (oxprenolol). All subjects had coronary arteriograms and left ventriculograms, and the results of exercise testing were related to the presence or absence of obstructive coronary artery disease. Possible causes of false positive exercise tests were eliminated by echocardiography. Though beta-blockade was unreliable in distinguishing ischaemic from non-ischaemic resting electrocardiograms, it eliminated all the false positive electrocardiographic responses to exercise in both groups and did not abolish any of the true positive electrocardiographic responses. Thus, specificity and predictive value were improved without reduction in sensitivity.

This technique may not necessarily be applicable to other groups of patients or to a random population, but the results of this study suggest it will be a useful additional routine procedure in the investigation of coronary heart disease.

The routine use of exercise testing to detect coronary heart disease remains controversial.[1–3] When applied to symptomatic patients with chest pain, where the prevalence of coronary heart disease is high, the reliability of this test is also high, but it may be argued that the diagnosis can usually be established by history alone. When applied to asymptomatic subjects, however, where the prevalence of the disease is low, the number of false positive results is high and consequently the specificity and predictive value (Table 1) of the exercise test are poor.[4–6] Positive exercise tests in asymptomatic apparently healthy persons, who have an electrocardiogram indistinguishable from that of myocardial ischaemia, present difficult problems familiar to those who use electrocardiography for routine screening and the exercise test as a further aid to diagnosis. The exercise test may then compound the problem rather than solve it.

Table 1 *Glossary of terms*

Sensitivity = percentage of all patients with disease who manifest an abnormal test

$$= \frac{TP}{TP + FN} \times 100\%$$

Specificity = percentage of negative results in subjects without the disease

$$= \frac{TN}{TN + FP} \times 100\%$$

Predictive value = percentage of positive results that are true positive

$$= \frac{TP}{TP + FP} \times 100\%$$

TP, true positive; FP, false positive; TN, true negative; FN, false negative.

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Received for publication 6 July 1979

The distinction between false and true positive exercise tests can be made only by coronary arteriography, but this is not usually performed in asymptomatic patients, not only because it is an expensive procedure with an element of risk, but also because precise diagnosis does not lead to specific treatment or improved prognosis. Where, however, an acute coronary event could place both patient and others at risk, precise diagnosis becomes essential. Public service vehicle drivers, pilots, and air traffic controllers are typical examples. The removal from duty of all asymptomatic pilots and air traffic control officers with positive exercise tests would eliminate many who are free from disease, highly trained, and experienced. Though the group with positive exercise tests appears at high risk of a coronary incident, there will be a greater absolute number of subjects who develop such incidents among the group with negative exercise tests because this population is much larger.[7] There has, therefore, been objection to the use of exercise testing as a screening device in asymptomatic personnel. It is difficult, however, to avoid the use of exercise testing in subjects with abnormal resting electrocardiograms; when such testing is positive, coronary arteriography becomes necessary to distinguish those with coronary heart disease from those without, if the subjects wish to continue in their profession. This indicates a clear need for an alternative, simple, and safe method for making this distinction.

A recent report[8] suggests that many fit, asymptomatic subjects, with normal coronary arteries and resting electrocardiographic changes indistinguishable from those of myocardial ischaemia, have a positive electrocardiographic response to exercise. The exercise-induced changes have been mimicked by low-dose adrenaline infusion combined with atrial pacing. Plasma catecholamine estimations in such persons indicate that the electrocardiographic features reflect altered response to normal adrenaline concentrations, rather than adrenaline hypersecretion. As beta-blockade is capable of blocking this adrenergic response, it seemed appropriate to investigate the effect of beta-adrenergic blockade on the electrocardiographic response to exercise.

Subjects and methods

One hundred men were investigated; 50 were patients presenting with angina and 50 were asymptomatic subjects with abnormal resting electrocardiograms suggesting myocardial ischaemia. Though subjects were selected for each group on the basis of angina or an abnormal electrocardiogram, there was no selection within the groups.

Group 1 contained 50 consecutive patients selected for coronary arteriography because of angina. All were men aged between 32 and 64 years (mean 48). Patients with evidence of previous myocardial infarction or whose electrocardiogram showed bundle-branch block or other conduction abnormality were not admitted to the study. None had evidence of valvar heart disease or systemic hypertension.

Group 2 contained 50 consecutive asymptomatic subjects referred for investigation of an abnormal resting electrocardiogram which showed ST-T changes indistinguishable from those of myocardial ischaemia. All were men aged 17 to 57 years (mean 37). Most were civilian or military aircrew or air traffic control officers who had undergone routine electrocardiography. Subjects with echocardiographic features suggesting cardiomyopathy, asymmetric septal hypertrophy, or prolapsing mitral valve were not included in the study. In no case was there any evidence of valvar heart disease, systemic hypertension, or conduction abnormality.

All subjects were admitted to hospital and were investigated as follows.

RESTING ELECTROCARDIOGRAPHY

Resting 12 lead electrocardiograms were recorded on a three-channel Mingograf Recorder, without prior medication and, on a separate occasion, one and a half to two hours after a single oral dose of 80 mg of the beta-adrenergic blocking agent oxprenolol (Trasicor). No subject received any medication except glyceryl trinitrate for three days preceding the study; digitalis, beta-adrenergic blocking agents, diuretics, and other drugs were omitted. Electrocardiograms were recorded in the lying and standing positions, during 30 seconds of hyperventilation, and during the Valsalva manoeuvre.

ECHOCARDIOGRAPHY

M-mode echocardiography was performed without beta-adrenergic blockade, using a Smith Kline Ekoline 20 A and a 2·25 MHz transducer focused at 7·5 cm, coupled to a Cambridge six-channel fibre-optic recorder. Recordings were made with the patient lying on his left side with the head of the bed raised to about 30 degrees.

The interventricular septal and left ventricular posterior wall echoes were recorded at both mitral and submitral level. The ratio of interventricular septal to left ventricular posterior wall thickness was considered abnormal if greater than 1·3, corrected for age.

TREADMILL EXERCISE TESTING

Maximal treadmill exercise tests were performed on each patient on two occasions using a three-channel Avionics monitor model 3000 and a computer programmer P100. The first test was performed without medication ('unblocked') and the second test one and a half to two hours after oral oxprenolol 80 mg ('blocked'). The adequacy of beta-blockade was confirmed by 15 to 20 per cent reduction in the resting and exercise heart rate. No subject received food or drink for three hours before the test. The procedure described by Bruce was adopted,[9] and the CM lead system was used to record three praecordial leads at the end of each stage and every minute during a 10-minute recovery period, with the subject recumbent. The three praecordial leads were positioned after inspection of the resting electrocardiogram in order to include lead positions where maximum changes had been observed. CM5 was included in each case. Blood pressure measurements were made using a cuff sphygmomanometer at rest, before exercise, 30 seconds before the end of each stage, and every minute during the recovery period. In one subject the treadmill exercise test was repeated on a third occasion after 160 mg oxprenolol, when 80 mg had failed to slow resting and maximal exercise heart rates by 15 per cent. The end-point was the limit of endurance, determined by fatigue, breathlessness, or severe chest pain, rather than target heart rate.

The criteria for a positive electrocardiographic exercise test were the development of, or an increase in, pre-existing ST segment depression of 1 mm or more relative to the TP segment, measured 80 ms after the nadir of the S wave in at least six consecutive beats, irrespective of whether the ST segment was upsloping, horizontal, or downsloping. A 'blocked' test was considered negative when there was less than 1 mm ST depression irrespective of the heart rate achieved. We also considered as negative those electrocardiographic responses which, though abnormal during the early stages of exercise and late recovery period, showed normal electrocardiographic configuration at maximum and near maximum heart rate.

CATHETERISATION STUDIES

Left heart catheterisation and coronary arteriography, by Sones or Judkins technique, were performed on all 100 patients. Left ventricular end-diastolic pressure was measured. Single plane left ventriculograms were obtained in the 30° right anterior oblique position at 40 frames per second, and coronary arteriograms were obtained in the anteroposterior, left anterior oblique, and right anterior oblique positions. Narrowing of coronary artery lumen by more than 50 per cent was considered obstructive. Coronary arteriography was performed within a month of the exercise test. No attempt was made to provoke coronary spasm.

Results

RESTING ELECTROCARDIOGRAPHY

Group 1

Thirty-four of the 50 patients with angina had abnormal resting electrocardiograms indicating myocardial ischaemia (ST segment and T wave changes). In eight of the 34 with ischaemic abnormalities the changes were greater in the standing position. Hyperventilation and the Valsalva manoeuvre produced inconstant effects.

After beta-blockade, 15 out of 34 abnormal electrocardiograms became normal (Fig. 1), eight improved but did not become normal, and 11 were unchanged. In the eight whose ischaemic abnormalities were exaggerated in the standing position, the postural effect was less after beta-blockade.

In this group, the resting heart rates ranged from 58 to 90 beats per minute (mean 70).

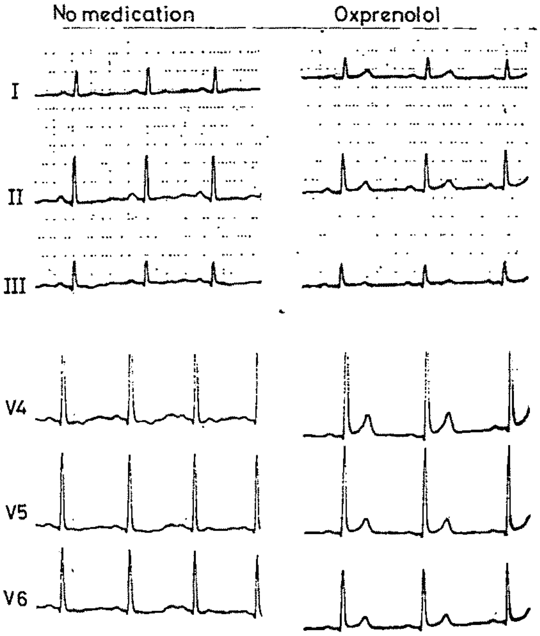

Fig. 1 *Resting electrocardiograms of a patient with angina and an abnormal coronary arteriogram. Left—abnormal, without medication.* Right—*normal, one and a half hours after 80 mg oxprenolol.*

Group 2

All 50 asymptomatic men had abnormal electrocardiograms on admission or during the previous six months. These changes included ST segment depression and/or low amplitude, flat, or inverted T waves. In 40 of the 50 men the abnormal electrocardiogram became normal after beta-blockade (Fig. 2), in eight it improved, and in two it was unaffected. In 15 out of 50 the changes were more prominent in the standing position and this postural effect was abolished by an oral dose of oxprenolol 80 mg (Fig. 3). Hyperventilation and the Valsalva manoeuvre produced variable and inconstant effects.

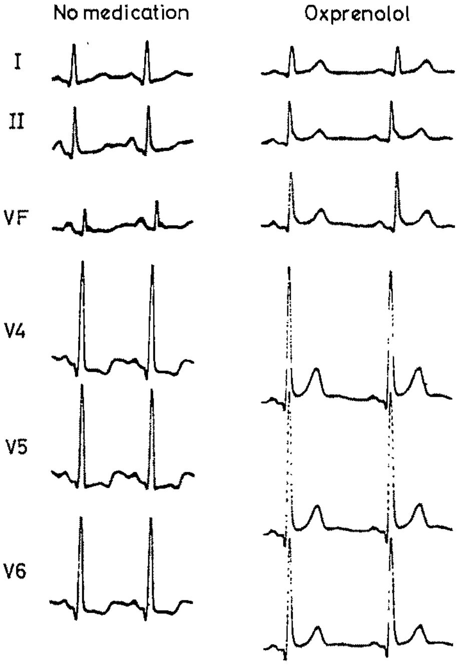

Fig. 2 *Resting electrocardiograms of an asymptomatic subject with a normal coronary arteriogram.* Left—*abnormal, without medication.* Right—*normal, one and a half hours after 80 mg oxprenolol.*

In this group, the resting heart rate ranged from 56 to 86 beats per minute (mean 75).

ECHOCARDIOGRAPHY

Group 1

No patient in this group showed disproportionate hypertrophy of the interventricular septum, narrow left ventricular outflow tract, or dynamic outflow tract obstruction with anterior mitral valve motion during systole. No patient showed echoes from prolapsing mitral leaflets. Eight patients had echocardiograms showing reduced interventricular septal or left ventricular posterior wall motion. The remaining 42 had normal echocardiograms.

Group 2

None of the 50 subjects had asymmetric septal hypertrophy, or other features to suggest cardiomyopathy or prolapsing mitral leaflets. However, in many of them the interventricular septum was found to be slightly thicker than in normal subjects of the same age though the difference was not significant.

EXERCISE TESTING

Group 1

As shown in Table 2, there was a definite positive

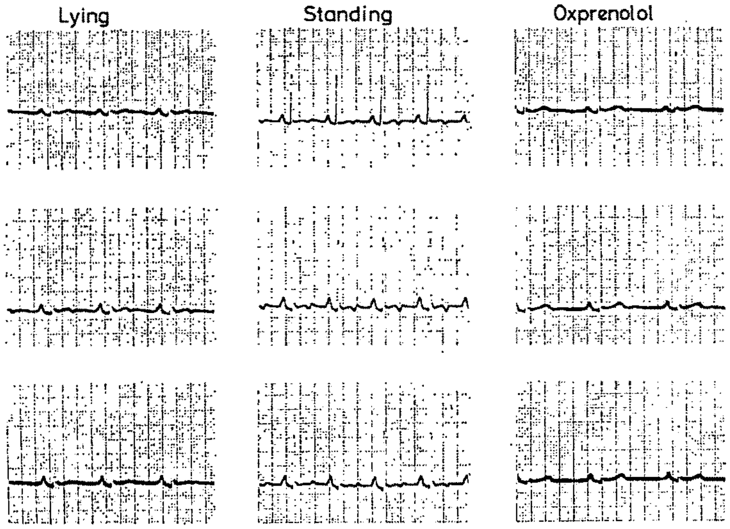

Fig. 3 *Effect of beta-blockade on postural changes in the resting electrocardiogram.* Left—*lying, without medication.* Centre—*standing, without medication.* Right—*standing, one and a half hours after 80 mg oxprenolol.*

electrocardiographic response in 'unblocked' tests in 44 of the 50 patients and a definite negative electrocardiographic response in the other six, no test being borderline. When the tests were repeated after oxprenolol, the responses remained positive in 43 and became normal in one. Coronary arteriography confirmed coronary heart disease in the 43 whose electrocardiographic response had remained positive after beta-blockade; the one whose response became normal had a normal coronary arteriogram, though the clinical diagnosis of angina was difficult to refute. In the 43 patients whose positive electrocardiographic response persisted after beta-blockade, the degree of the ST segment depression was usually reduced (Fig. 4). The closest approximation to a normal exercise electrocardiogram in this group of 43 patients is illustrated in Fig. 5, though, with strict application of the defined criteria, even this test remained unequivocally positive. The six negative electrocardiographic responses to the 'unblocked' exercise test remained negative after beta-blockade.

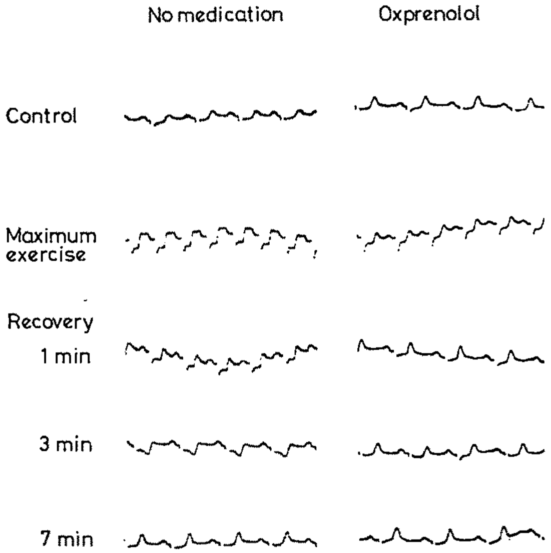

Fig. 4 *Exercise electrocardiograms of a patient with angina and an abnormal coronary arteriogram. Left—positive electrocardiographic response, without medication.* Right—*positive electrocardiographic response, one and a half hours after 80 mg oxprenolol.*

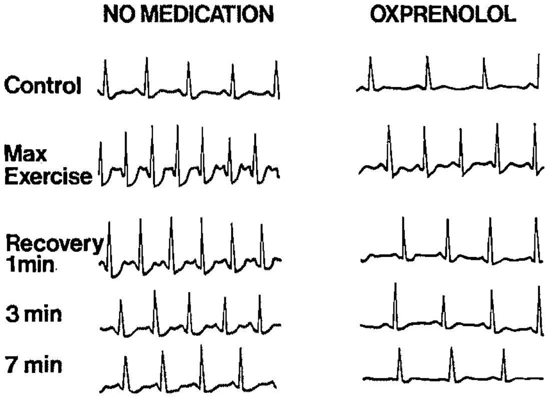

Fig. 5 *Exercise electrocardiograms of a patient with angina and an abnormal coronary arteriogram. Left—positive electrocardiographic response, without medication.* Right—*positive electrocardiographic response, one and a half hours after 80 mg oxprenolol.*

Group 2

As shown in Table 3, a positive electrocardiographic response to exercise was recorded in 'unblocked' tests in 20 of the 50 subjects and a negative response in 30. When the test was repeated after beta-blockade, the electrocardiographic response became normal in 19 out of the 20 (Fig. 6) and in these 19 the coronary arteriogram was subsequently shown to be normal. In the remaining one, however, the electrocardiographic response to exercise remained positive, though the degree of ST segment depression was reduced. The 30 negative 'unblocked' tests were unaffected by beta-blockade, and coronary arteriography confirmed the absence of obstruction. In eight of these 30 negative responses, the electrocardiogram was abnormal during the beginning of the 'unblocked' test, became normal during exercise, and returned to the original abnormal pattern during the recovery period. However, beta-blockade abolished these electro-

Table 2 *Group 1: Exercise test results on 50 patients with angina*

No medication	*Oxprenolol*
44+ve (43 TP+1 FP) 6−ve (3 TN+3 FN)	43+ve (43 TP+0 FP) 7−ve (4 TN+3 FN)

TP, true positive; FP, false positive; TN, true negative; FN, false negative; +ve, positive; −ve, negative.

Table 3 *Group 2: Exercise test results on 50 symptomless subjects with abnormal electrocardiogram*

No medication	*Oxprenolol*
20+ve (1 TP+19 FP) 30−ve (29 TN+ 1 FN)	1+ve (1 TP+0 FP) 49−ve (48 TN+1 FN)

Abbreviations as in Table 2.

cardiographic changes, and the test became normal throughout (Fig. 7). The end-point of exercise (limit of endurance) was in many cases beyond the point of the age-predicted maximal heart rate.

One subject was of particular interest. This 30-year-old asymptomatic man with unobstructed coronary arteries had a positive electrocardiographic response to exercise before and after oxprenolol. However, the resting heart rate before the second test was not significantly decreased, suggesting inadequate blockade. In fact, this man had shown exceptional sensitivity to adrenaline infusion in a separate study. Because of these observations, treadmill exercise was repeated a third time, after oxprenolol 160 mg. The resting heart rate then slowed and subsequent exercise tracings were all completely normal (Fig. 8).

CATHETER STUDIES

Group 1

Coronary arteriography showed that 46 of the 50 subjects had at least 70 per cent arterial narrowing in one or more vessels. Of these 46 with coronary heart disease, 43 had a positive electrocardiographic response to exercise after blockade, and three had false negative responses. Of the 43, eight had three-vessel disease, 17 had two-vessel disease, and 18 had one-vessel disease. Of the three with false negative electrocardiographic responses to exercise, one had two-vessel disease and two had one-vessel disease. The one patient whose positive electrocardiographic response to the 'unblocked' test was normal after beta-blockade, together with the remaining three with negative electrocardiographic responses to 'blocked' tests, had normal coronary arteries.

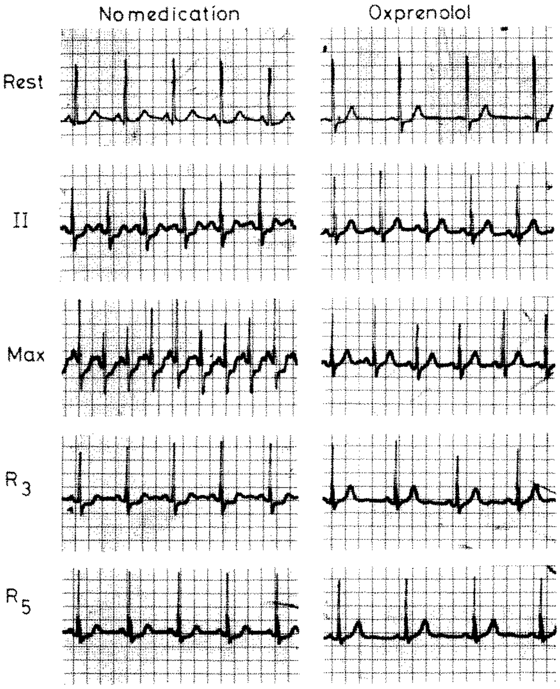

Fig. 6 *Exercise electrocardiograms of an asymptomatic subject with a normal coronary arteriogram.* Left—*positive, without medication.* Right—*negative, one and a half hours after 80 mg oxprenolol.*

Group 2

Coronary arteriography showed that two out of the 50 subjects with abnormal electrocardiograms had

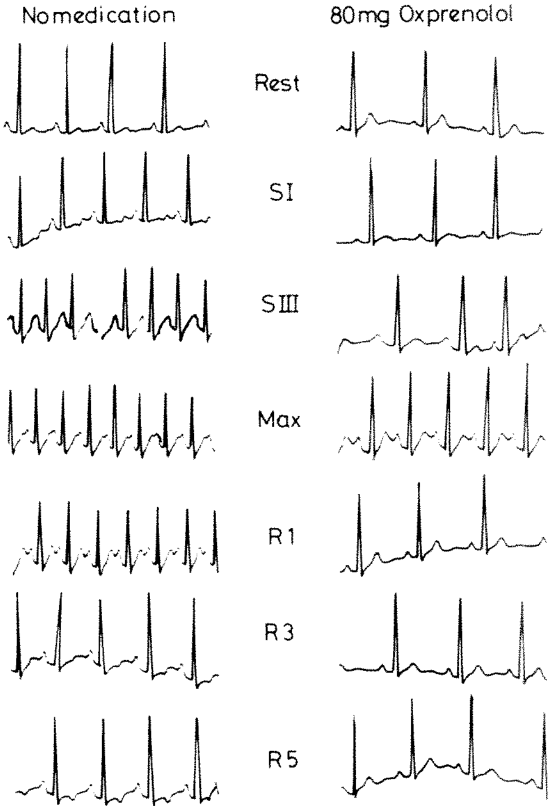

Fig. 7 *Exercise electrocardiograms of an asymptomatic subject with a normal coronary arteriogram.* Left—*electrocardiographic changes during early and recovery phases, negative at maximum, without medication.* Right—*negative, one and a half hours after 80 mg oxprenolol. S, stage of exercise procedure; R, recovery period.*

obstructed coronary arteries. One of these two had positive electrocardiographic responses to exercise both before and after beta-blockade, and coronary arteriography showed 80 per cent proximal narrowing of the right coronary artery, 80 per cent stenosis of the circumflex, and a minor lesion in the anterior descending coronary artery. The other one had a negative electrocardiographic response to exercise both before and after beta-blockade; this was a false negative response, as coronary arteriography revealed 70 per cent narrowing of his right coronary artery. Of the remaining 48, 47 had normal coronary arteries, and one had an obstruction of less than 50 per cent of his left anterior descending coronary artery.

Discussion

The risk, high cost, and discomfort of coronary arteriography make it an unsuitable procedure for general use. Therefore, the development of reliable non-invasive methods for the detection of myocardial ischaemia remains one of the more important challenges for diagnostic cardiology. High sensitivity and specificity for the detection of myocardial ischaemia have been claimed for thallium-201 myocardial imaging,[10 11] though not in all reports,[12] and application is limited by cost of both imaging agent and imaging apparatus. The technique will probably be more widely used, but the improvement of existing inexpensive methods would be of more immediate value.

Responses to exercise other than electrocardiographic changes have been assessed.[13 14] These include the symptomatic response to exercise, the development of anginal pain,[14] and the haemodynamic response, blood pressure and heart rate changes.[15 16] Attempts to increase the reliability of the test have recently been made,[17–19] using such multivariate criteria. There is no doubt that these methods will further increase the accuracy of exercise testing. However, this study is concerned only with the electrocardiographic response to exercise.

The specificity of the electrocardiographic response to maximal exercise testing for detection of myocardial ischaemia, using both epidemiological and coronary arteriographic methods of control, is 90 to 93 per cent.[20–22] Any test which falsely identifies up to 10 per cent of subjects as having coronary artery disease has serious limitations as a screening method, especially when those subjects depend on a normal result for their livelihood. Various methods have therefore been used in an attempt to improve the diagnostic accuracy of electrocardiographic response to exercise. For example, increasing the workload improves sensitivity, but results in a higher number of false positive tests because of the inverse relation between sensitivity and specificity in all forms of exercise testing; similarly, changing the criterion for positivity from 1 to 2 mm ST segment depression results in an increase in specificity but a decrease in sensitivity.

Electrocardiographic ST and T wave changes occurring at rest may be caused by several organic and non-organic conditions. They may result from coronary heart disease and other organic conditions,

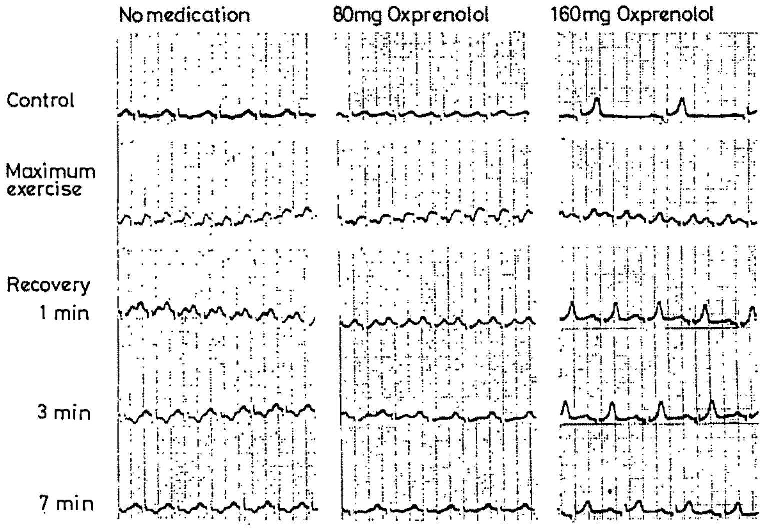

Fig. 8 *Exercise electrocardiograms of an asymptomatic subject with a normal coronary arteriogram.* Left—*positive, without medication.* Centre—*positive, one and a half hours after 80 mg oxprenolol.* Right—*negative, one and a half hours after 160 mg oxprenolol.*

or they may be functional as in neurocirculatory asthenia[23], the hyperkinetic heart syndrome,[24] postural changes,[25] hyperventilation,[26] and emotion.[27] Beta-blockers can lessen and sometimes abolish these resting electrocardiographic changes irrespective of their cause, as has been shown when these result from coronary atherosclerosis,[28] the hyperkinetic heart syndrome,[24] hyperventilation,[29] postural changes,[30] or emotion. The ability of propranolol to abolish functional ischaemic-like electrocardiographic resting changes in the absence of coronary heart disease has also been described.[31–33] However, none of the patients had coronary arteriograms, and classification was based purely on clinical criteria. Furthermore, this otherwise similar group of subjects with dominant sympathetic hyperactivity is in striking contrast to our group 2, in whom resting heart rate was low.

Several possible causes of false positive electrocardiographic response to exercise must be excluded if the specificity for coronary heart disease is to be increased. These include hypertrophic cardiomyopathy, asymmetric septal hypertrophy, and prolapsing mitral valve,[3 17] and patients with these conditions were excluded by echocardiography before this study. Other causes such as digoxin or other drugs, metabolic disturbances such as hypokalaemia, conduction abnormalities, and the syndrome of vasoregulatory asthenia were also excluded. In this study of men it is not necessary to consider other causes of false positive response to exercise which occur predominantly in women.

In this study, oxprenolol reversed many, but not all, of the resting electrocardiographic abnormalities of group 1 patients with obstructed coronary arteries. Oxprenolol also reversed many, but again not all, of the resting electrocardiographic changes of group 2 subjects with normal coronary arteries. It is obvious from these observations that, on the basis of its effect on the resting electrocardiogram, beta-blockade is not useful for identifying patients with coronary heart disease.

The effect of beta-blockade on the electrocardiographic response to exercise, however, was different. In patients with angina (group 1), oxprenolol had no effect on the true positive electrocardiographic response to exercise of the 43 patients with obstructed coronary arteries, but did restore to normal the exercise electrocardiogram of the single patient whose coronary arteriogram was subsequently shown to be normal. It thus improved the specificity from 75 to 100 per cent and the predictive value from 98 to 100 per cent without reducing the sensitivity, which remained at 93 per cent (Table 4).

In group 2, oxprenolol restored to normal all the 19 false positive electrocardiographic responses to exercise, but not the response of the one patient with significant coronary artery obstruction. The specificity was thus increased from 60 to 100 per cent and the predictive value from 5 to 100 per cent. The sensitivity, at 50 per cent, remained unchanged (Table 4). In no case did beta-blockade abolish the true positive electrocardiographic response to the exercise test. It should be noted that, while at the maximal heart rate after beta-blockade the electrocardiographic response to exercise was negative, at the corresponding heart rate during the 'unblocked' test it was positive, indicating that the electrocardiographic improvement was not a heart rate effect (Fig. 9).

In group 2, eight out of 30 who had a negative electrocardiographic response to exercise had an abnormal electrocardiogram before, and during early phases of, the 'unblocked' exercise test; the electrocardiogram became normal at maximum exercise and returned to abnormal during the late recovery period. These tests were regarded as

Table 4 *Sensitivity, specificity, and predictive value in groups 1 and 2 before and after beta-blockade*

	No medication	*Oxprenolol*
Group 1: 50 patients with angina		
	(%)	(%)
Sensitivity	93	93
Specificity	75	100
Predictive value	98	100
Group 2: 50 symptomless subjects with abnormal electrocardiogram		
	(%)	(%)
Sensitivity	50	50
Specificity	60	100
Predictive value	5	100

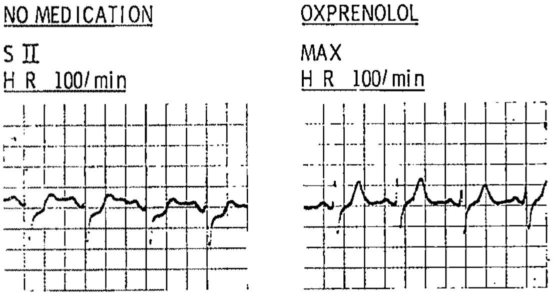

Fig. 9 *Exercise electrocardiograms of an asymptomatic subject with a normal coronary arteriogram.* Left—*positive at HR 100/min, without medication.* Right—*negative at HR 100/min, one and a half hours after 80 mg oxprenolol. S, stage of exercise procedure; HR, heart rate.*

negative because it is unlikely that, in the presence of coronary artery obstruction, the electrocardiogram could become normal with increasing heart rate and oxygen demand. We have seen no such electrocardiographic response in patients with coronary heart disease nor, to the best of our knowledge, has it been reported. However, even if this type of response is classified as positive, the subsequent exercise test after beta-blockade was normal throughout in these patients. Our findings are in agreement with those of Furberg[31] and Kattus *et al.*[30] who found that beta-blockade did not abolish electrocardiographic abnormalities in patients with organic disease on exercise, but did abolish resting electrocardiographic abnormalities when these were functional. These data lead to the conclusion that beta-blockade will abolish a false positive electrocardiographic response to exercise but will not affect a true positive response.

The use of exercise testing for detection of myocardial ischaemia in patients with abnormal electrocardiograms at rest, similar to our group 2, has been recently reported by Surawicz and Saito[34]; however, they did not use beta-blockade in such patients with false positive tests.

Our results are in keeping with the hypothesis of Taggart *et al.*[8] that the electrocardiographic changes resembling myocardial ischaemia in the presence of normal coronary arteries are the result of altered myocardial sensitivity to normal levels of circulating catecholamines. They showed that exercise-induced electrocardiographic changes resembling those of ischaemia may be mimicked by adrenaline infusion, and now it appears that they may be blocked by beta-blockade.

The groups reported in this study were small, and more cases must be investigated to establish what effect beta-blockade has on the electrocardiographic response to exercise of those who present with pain resembling angina but with normal coronary arteries. It is also premature to extrapolate from group 2, consisting of asymptomatic individuals with abnormal resting electrocardiograms, to patients with coronary heart disease who do not have chest pain. The number of patients with coronary heart disease in our group 2 was small, and further work is in progress to confirm our initial findings. Furthermore, the two groups of patients presented here were selected, so that it is inappropriate to apply any conclusions to a random population. However, if our observations are confirmed, the need for coronary arteriography will be much reduced, both in symptom-free people with abnormal resting electrocardiograms and in symptomatic individuals with normal or abnormal resting electrocardiograms and positive electrocardiographic response to exercise. The procedure described should then become routine in the investigation of coronary heart disease.

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Br Heart J 1980; **43**: 262–269

Effects of physical training on myocardial ischaemia in patients with coronary artery disease

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SUMMARY The effects of a simple physical training programme were investigated in a prospective and randomised trial in patients with stable angina pectoris using a modified exercise test. Twenty-four patients with ischaemic heart disease and an ischaemic response to conventional exercise electrocardiography were randomised into two groups: 12 patients took part in a training programme and 12 patients were allocated to a control group (no training). Exercise testing was performed sequentially at entry to the study and six months afterwards. At both studies we determined the heart rate at the same level of ischaemic ST segment depression (HR/ST threshold), the duration of the test, and relation of heart rate to the exercise load.

The HR/ST threshold increased only in patients who underwent the exercise programme, suggesting indirectly that training resulted in the ability to do more work and attain a higher degree of myocardial oxygen consumption at the same level of myocardial ischaemia. In addition, training led to an increase in the duration of the test and to a reduction in heart rate at any level of submaximal exercise load.

It is concluded that physical training in anginal patients results in an enhancement of myocardial oxygen availability.

Clinical exercise testing has been extensively used to provoke electrocardiographic changes attributed to ischaemia and to assess changes in functional capacity in patients with ischaemic heart disease,[1 2] and, by serial exercise testing, to assess the results of physical training programmes.[2–4] However, most of these studies have been limited to the consideration of improvement in exercise capacity, or the consequences of the reduction in heart rate and blood pressure at a given level of exercise, that is the ability to perform more work before the onset of angina at the same heart rate and blood pressure.[2 5 6] A relatively smaller number of studies have investigated levels of heart rate and blood pressure during myocardial ischaemia using subjective criteria, for example anginal pain,[5–7] thus investigating the ability to perform more work and attain a higher heart rate and blood pressure at the occurrence of anginal pain.

In this report, the effect of a convenient physical training programme known to improve cardiorespiratory fitness was investigated in patients with stable angina pectoris.[8] A modified exercise test relating levels of heart rate and systemic blood pressure to an objectively determined level of myocardial ischaemia was shown to be sensitive enough to detect improvement in the ability to attain a higher heart rate and blood pressure at the same objective level of myocardial ischaemia.

Subjects and methods

Twenty-four patients in whom the diagnosis of stable angina pectoris was confirmed by obtaining an ischaemic response during exercise electrocardiography in each, and in addition by selective coronary arteriography in 11 patients, were selected for the investigation. Patients with hypertension, valve disease, cardiac arrhythmia, and patients on digoxin, beta-blocker, or nifedipine therapy were excluded from the study.

On entry to the study, the patients were randomised into two groups. One group consisted of 12

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Received for publication 29 August 1979

patients (10 men and two women) who undertook a six-month programme of physical training. The remaining 12 patients (11 men and one woman) did not participate in the training programme but continued their normal daily activities. Clinically, the two groups were managed identically by the consultant cardiologist (WW). Each patient was advised to stop smoking and avoid increases in body weight. All patients were followed-up independently in the cardiology outpatient clinic and whenever deemed necessary on clinical grounds their management was modified according to the routine practice by the consultant cardiologist (WW). Thus, in each patient trinitrate therapy alone was adequate at the entry to the study to control anginal pain. However, during the period of study, beta-blocker or nifedipine therapy was instituted when the patient developed deterioration of anginal symptoms as judged independently by the cardiologist (see results). At the time of entry to the investigation and at the end of six months the patients were studied using an exercise electrocardiography test.

EXERCISE TEST

The exercise test was performed on an electrically braked bicycle ergometer (Elema Schonander, type 380) with the patients in the upright posture. The patients pedalled at 60 rpm against a continuous series of incremental loads; the initial load being 150 kpm/min. The workload was increased in steps of 150 kpm/min at three-minute intervals. The end point of the test was defined as the occurrence of ischaemic ST segment depression on an electrocardiogram recorded from CM5 position. The heart rate (beats/min) was obtained from the electrocardiogram during the last minute of every workload, when it attained a constant level. After a 40-minute rest period, the patients performed a second test in which incremental workloads, each of three minutes' duration, were separated by rest periods. The initial load was the same as that which, in the previous test, resulted in the highest heart rate response before the onset of ischaemic ST depression. Subsequent loads were increased in smaller steps of 25 kpm/min so as to effect a smaller step increase in heart rate; such a technique allowed a more accurate estimation to be made of the lowest heart rate response at which an ischaemic ST depression occurred. The systemic blood pressure was measured in the left arm using an electronic sphygmomanometer (Elag-Koln) at each load when the heart rate had reached a steady value.

The occurrence of ischaemic ST segment depression which indicated the end point of the test was defined as a net ST segment depression of 0·1 mV, at 80 ms after the J point of the electrocardiogram,[9] in the presence or absence of anginal pain. The heart rate (HR) and the product of heart rate and systolic blood pressure (RPP) at this end point were termed the HR/ST threshold and RPP/ST threshold, respectively. This end point also determined the point at which the duration of the continuous test in minutes was measured. The heart rate/load relation was expressed in terms of computed regression lines.

TRAINING PROGRAMME

The patients randomised into the training group undertook the Canadian Air Force programme (5BX/XBX) under supervision in the hospital. This programme was considered suitable since it required only 11 to 12 minutes of daily physical training, and since it has been shown to improve cardiorespiratory fitness in normal subjects,[8] and in patients after cardiac surgery.[10] The programme lasted six months, and during hospital sessions the patients exercised with electrodes attached in CM5 position. The patients started training at the lowest physical capacity level, and progressed by increasing this level according to their age and sex.[11] If the level of exercise was well tolerated the patient was asked to perform the same level at home during the week and return so that the level could be adjusted under supervision. If, during the performance of an increased level of exercise, anginal pain and/or ischaemic ST depression occurred, the patients were maintained at the previous level of exercise.

REPEATABILITY OF TEST

The tolerance limits of the measurements of HR/ST threshold were studied in five patients. After a preliminary test to familiarise the patient, three successive tests were performed on three consecutive days, and the HR/ST thresholds obtained were used for analysis of repeatability of the test, in a blinded fashion as was previously described[9]; all tracings were copied and the five used in the repeatability tests were randomly interspersed by a person other than the observer.

Results

Initially, changes in both heart rate and systolic blood pressure (SBP) were analysed in terms of HR/ST threshold and RPP/ST threshold. However, the initial values of SBP at the onset of ischaemic ST segment (176 mmHg mean; range 155 to 210 mmHg) were not different ($2p > 0{\cdot}20$; paired t test) from those obtained at the end of the study (171 mmHg mean; range 150 to 210 mmHg). Therefore, the heart rate alone was used to analyse the results, rather than RPP. Thus, in the presence of an unchanged SBP, the use of heart rate alone would first have the relative virtue of being measured to a recognised accuracy from the electrocardiogram. Secondly, the sensitivity of the test relates basically to the level of heart rate, since at the last incremental load step during the discontinuous test only heart rate changes were observed, SBP remaining constant in the face of small load increments. Finally, analysis of individual changes in rate-pressure product yielded results which were effectively the same as those from heart rate measurement alone (Tables 1 and 2).

Table 1 *Exercise testing in 12 patients after physical training*

Subject	*Duration of test (min)*		*Submaximal* HR/load regression analysis*	*Heart rate/ST threshold (beats/min)*		*Rate-pressure product† 10^{-2}*	
	Initial	*Final*		*Initial*	*Final*	*Initial*	*Final*
MP	6	15	+	110	140	24·3	33·5
EC	16	18	–	130	140	27·7	31·7
EH	12	15	–	95	130	20·2	27·7
RH	6	10	+	112	120	25·3	27·1
FL	12	16	–	130	140	26·8	33·5
RS	12	17	+	128	130	34·0	36·3
MW	5	6	–	120	122	23·9	24·3
TS	12	15	+	150	150	30·9	29·9
HR	15	15	–	130	132	31·1	31·6
VF	12	15	+	150	150	34·9	35·9
JM	15	15	–	145	145	40·5	34·7
GL	12	12	–	115	114	24·5	24·3

*+ = Statistically significant decrease in elevation of HR/load regression line ($p < 0·005$ to $p < 0·025$).
– = No change in slope or elevation of HR/load regression line.
†Product of HR (beats/min) × SBP (kPa). Conversion factor to mmHg, 7·52.

Table 2 *Exercise testing in control group of five patients**

Subject	*Duration of test (min)*		*Submaximal* HR/load regression analysis*	*Heart rate/ST threshold (beats/min)*		*Rate-pressure product† 10^{-2}*	
	Initial	*Final*		*Initial*	*Final*	*Initial*	*Final*
JT	9	9	–	130	125	32·9	29·9
FC	12	12	–	130	125	34·7	26·6
KF	9	6	–	130	125	34·7	28·3
JW	13	12	–	140	135	36·3	30·5
JK	12	9	–	120	120	25·5	25·5

*Abbreviations as in Table 1.
†Units as in Table 1.

REPEATABILITY OF RESULTS

In the measurement of HR/ST threshold, the results showed that using the continuous exercise test procedure the increase in heart rate between the subthreshold load step and the end point of the test was larger in patients before training than after training. Thus step increases in heart rate averaged 22·1 beats/min (range 10 to 40) before training and 16·2 beats/min (range 5 to 38) after training. In order to avoid the error expected from such large step increases in heart rate, the HR/ST threshold was also studied using the discontinuous test with smaller load increments; the corresponding steps of increases in heart rate averaged 7 beats/min (range 5 to 20).

In five patients the HR/ST threshold was estimated repeatedly, three times over three consecutive days (Table 3). In any given patient the difference in HR/ST threshold ranged from 0 to 2 beats/min. The 95 per cent tolerance limit with 95 per cent confidence of the deviations of measurement from the mean was 2·5 beats/min.

Table 3 *Heart rate/ST threshold obtained from three repeated measurements on three consecutive days in five patients*

Subject	*Exercise test day*			*Mean*	*SD*
	1	*2*	*3*		
JK	120	118	120	119·3	1·2
GL	110	108	110	109·3	1·2
MW	122	121	123	122·0	1·0
FL	140	138	140	139·3	1·2
JM	145	145	145	145·0	0·0

EFFECT OF TRAINING

All 12 patients in the training group completed the physical training programme uneventfully and in each patient exercise testing was performed before and after physical training (Table 1). All the patients had an ischaemic ST segment response during the post-training test. However, while ischaemic ST segment depression was associated with anginal pain in 11 patients before training, only four had anginal pain at the end point of the exercise test after training. Changes in submaximal heart rate/load relation in every patient were studied using analysis of covariance to detect statistically significant changes in the slope or elevation of the relationship's regression line.[12] In five patients there was a statistically significant reduction in the elevation of the submaximal heart rate/load regression line (p from $< 0·005$ to $< 0·025$). In the remaining seven patients the reduction did not reach statistical significance. Nine patients achieved a longer duration of test after training; the increases averaged 2·8 min (range 1 to 9). In the remaining three patients the duration of the test did not change. Considering the whole group, the increases in test duration were statistically significant ($2p < 0·005$; paired t test).

The HR/ST threshold increased in eight patients by an average of 12·4 beats/min (range 2 to 35), did not change in three patients, and decreased in the remaining patient. The increase in threshold after training compared with the threshold before training was statistically significant ($2p < 0{\cdot}05$; paired t test).

CONTROL GROUP

In seven of the 12 patients in the control group an independent decision to start medical treatment with drugs was made during routine cardiological follow-up on the basis of deterioration of symptoms. Exercise tests were therefore performed sequentially in five patients on entry to the study and after six months (Table 2). During this period the patients continued their normal daily activities. In all five patients anginal pain accompanied ischaemic ST segment depression during the initial and final tests. The heart rate/load relation did not change either in elevation or slope of the regression line in any of the five patients. The duration of the test decreased by three minutes in two patients, by one minute in one patient, and did not change in the remaining two patients.

The HR/ST threshold decreased in four patients by 5 beats/min and was unchanged in the remaining patient. These changes in all five patients were statistically significant ($2p < 0{\cdot}02$; paired t test).

SIMILARITY BETWEEN GROUPS

The results of the initial tests, that is at the start of the investigation, in the training group were similar to those in the control group (Table 4). Thus the differences in duration of the test, in HR/ST threshold, and in RPP/ST threshold were not statistically significant ($2p > 0{\cdot}7$; $2p > 0{\cdot}70$; $2p > 0{\cdot}20$, respectively; unpaired t test). The training group comprised 10 men and two women, and their ages averaged 51 years (range 28 to 60). The control group (non-training) consisted of 11 men and one woman, and their ages averaged 49 years (range 40 to 57). The ages of both groups were similar ($2p > 0{\cdot}40$; unpaired t test). A history of previous myocardial infarction was present in three patients of the training group and in one patient of the control group. Coronary arteriography was performed in six patients who undertook the training programme and in five patients of the control group. The number of diseased vessels in these patients was similar in both groups (Table 4).

The similarity in the initial response to exercise testing (exercise duration, HR/ST threshold, and RPP) was maintained (Table 5) when the training group was compared with five patients in the control group who completed the study ($2p > 0{\cdot}80$; $2p > 0{\cdot}50$; $2p > 0{\cdot}10$, respectively; unpaired t test). The control group comprised four men and one woman and their ages averaged 47 years (range 45 to 50). The difference in age between the resulting control group and the training group was not significant ($2p > 0{\cdot}10$; unpaired t test). The similarity in findings of coronary arteriography and the incidence of previous myocardial infarction between the two groups of patients was also maintained (Table 5).

Discussion

Physical training has been used with increasing frequency in the management of patients with angina pectoris; effects of training such as improvement in functional capacity and sense of well-being have been reported.[2 13] However, the evidence for direct regression in the level of myocardial ischaemia has not been consistent. While there is experimental evidence from animals indicating improvement in mechanical, vascular, and biochemical characteristics of the myocardium,[14–18] clinical studies in which left ventricular function, myocardial vascularity, and blood flow were assessed during cardiac catheterisation and angiocardiography have yielded variable results partly because of the uncertainty regarding the sensitivity of the methods used to detect increased blood flow in local ischaemic regions of the myocardium and the difficulty of applying such invasive methods during exercise.[6 19–21] Non-invasive techniques such as exercise testing can be used to provoke ischaemic ST segment changes in the electrocardiogram or anginal symptoms and in addition provide a basis for quantitative evaluation of changes in physical capacity and cardiocirculatory response.[1 2 7 22 23] Exercise electrocardiograph testing has therefore been extensively used to investigate two main potential effects of training; an improvement in work capacity leading to a delayed onset of anginal

Table 4 *Data relating to 24 patients at entry to study*

Group	*Sex (male-female)*		*Age* (y)*	*Previous myocardial infarction*	*Coronary lesions‡*		*Duration of exercise* (minutes)*	*HR/ST threshold* (beats/min)*	*Rate-pressure product† 10^{-2}**
					1 vessel	*2 vessels*			
Training	10	2	28–60 (51)	3	5	1	5–16 (11·3)	95–150 (126·3)	20·2–40·5 (28·7)
Control	11	1	40–57 (49)	1	4	1	9–13 (10·8)	110–150 (128·2)	22·9–37·9 (31·2)

*Range (mean). †Units as in Table 1. ‡Luminal obstruction of > 75 per cent in any of the anterior descending, circumflex and the right coronary artery.

symptoms and a direct improvement in myocardial oxygen supply, that is the onset of ischaemic pain at a higher level of myocardial demand.[2–7, 13, 19, 24, 25]

In the investigations reported above, at least three clinically accessible responses to exercise have been considered. First, circulatory responses were measured in terms of heart rate, systemic blood pressure, and left ventricular ejection time. Secondly, exercise capacity was evaluated as the duration of the test, intensity of workload, and/or total oxygen consumption. Thirdly, the extent of any level of ST segment depression was taken to indicate an ischaemic response. However, the occurrence of anginal pain during the exercise test was used as the end point at which these responses were investigated.[2, 4–7] The use of such a subjective reference point suffers from obvious limitations. Distinct variations occur in the duration of the test and heart rate at the onset of angina.[26] Furthermore, the results of the present study and those of others[5] show that the relation between the occurrence of angina and ischaemic ST depression can be altered after physical training; after physical training, only four out of 11 patients in this study continued to complain of angina at the onset of ischaemic ST depression. From this evidence a cause and effect relation between training and a delayed onset of subjective appreciation of anginal pain is difficult to confirm or deny. It is obvious, however, that the recognised occurrence of such a subjective factor would lead to false conclusions of an improvement in terms of a higher work capacity or a higher circulatory response.

The evidence for an improvement in work capacity stems from objective studies in which submaximal reference points have been chosen either in terms of load intensity, heart rate, or oxygen consumption.[3–5, 19, 25] Using a symptom-limited test, it is to be expected that the heart rate and systemic blood pressure after a training period would be lower at any given level of exercise, thereby enabling a higher intensity and duration of exercise to be achieved before the onset of angina, that is the improvement in patients with a limited myocardial oxygen supply is the result of a lower myocardial oxygen demand at any given level of exercise.[2, 27] Such observations do not objectively confirm or deny a direct improvement in myocardial 'oxygen supply', that is the possibility that physical training results in an improvement in myocardial oxygen supply, in that the patients gain the ability to do more work at a higher myocardial oxygen demand before the objective occurrence of myocardial ischaemia.

To our knowledge the present investigation is the first to provide objective evidence indicating improvement in myocardial 'oxygen supply' after a period of physical training in patients with angina pectoris. It is suggested that this improvement was shown as a higher heart rate during exercise testing which occurred at an objectively determined level of myocardial ischaemia in terms of the widely accepted ischaemic depression of the ST segment in the electrocardiogram.[9] While known determinants of myocardial oxygen consumption include heart rate, ventricular pressure, size, ejection time, and contractile behaviour,[28, 29] heart rate alone provides a simple, reliable measurement in the non-invasive clinical setting. It has been shown to be a fairly accurate correlate of myocardial oxygen demand during upright exercise.[30, 31] The heart rate in this context provides an integral of developed left ventricular wall tension, systolic pressure, and dynamic muscle behaviour over a period of one minute.[29] Thus, during sequential exercise testing an increase in HR/ST threshold indicates an improvement in oxygen supply since it reflects a higher level of myocardial oxygen demand at the same level of myocardial ischaemia. Conversely, a decrease in this threshold indicates decreased oxygen supply.

It is implicit in these considerations that an increase in HR/ST threshold alone can indicate an improvement in the ability to attain a higher myocardial oxygen demand only if the systolic blood pressure, left ventricular wall thickness, size, contractile behaviour, and ejection time were not reduced by physical training. In respect of systolic blood pressure, the present results have shown that training was not associated with significant changes in systolic blood pressure, as has also been reported in patients with angina pectoris.[2] Heart

Table 5 *Data at entry to study, relating to 17 patients in whom a complete sequential investigation was possible*

Group	*Sex (male-female)*		*Age* (y)*	*Previous myocardial infarction*	*Coronary lesions‡*		*Duration of exercise* (minutes)*	*HR/ST threshold* (beats/min)*	*Rate-pressure product† 10^{-2}**
					1 vessel	*2 vessels*			
Training	10	2	28–60 (51)	3	5	1	5–16 (11·3)	95–150 (126·3)	20·2–40·5 (28·7)
Control	4	1	45–50 (47)	1	3	1	9–13 (11·0)	120–140 (130·0)	25·5–36·3 (32·8)

*Range (mean). †Units as in Table 1. ‡As in Table 4.

rate alone or heart rate-pressure produce has been shown to correlate better with myocardial oxygen consumption than did the product of systolic blood pressure, heart rate, and ejection time during upright exercise in normal subjects.[31] Thus, while the relative importance of systolic ejection period in the determination of myocardial oxygen consumption remains unsettled,[29] this period has been shown to increase during exercise after training in normal subjects[32] and in anginal patients[22]; the duration of the ejection time is now thought to be of minor importance in estimating myocardial oxygen consumption. Physical training in the dog has been shown to result in an increase in left ventricular wall thickness in the absence of a significant change in the end-diastolic volume at rest.[33] An increase in left ventricular wall thickness and in end-diastolic dimensions at rest has been reported in normal subjects after training.[34] Wallace *et al.*[35] used radionuclide angiography to show that physical training in 12 anginal patients resulted in an increase in end-diastolic volume at rest and during exercise testing. The effect of training on left ventricular contractility during exercise in anginal patients is not known but is unlikely to be different from the above. Therefore, the present use of an increase in heart rate at the onset of ischaemic ST segment depression as an indicator of increased myocardial oxygen demand is acceptable for sequential studies in a given subject. The present study has shown that the measurement of the HR/ST threshold is reproducible in a given patient; the maximum variation in heart rates during repeated measurements did not exceed 2 beats/min. Such a finding is an essential requirement before using this theshold in individual patients. This adequate reproducibility was achieved by a simple exercise test using small step increases in heart rate. An alternative method of ensuring objectivity in measurement would be to use the more sophisticated and complicated computer technique.[36]

Accepting that an increase in HR/ST threshold indicates improvement in myocardial blood supply, that is improvement in the ability to do more work at a higher heart rate before the occurrence of ST segment depression, it is considered that the present results show that physical training is associated with a direct improvement in myocardial blood supply. For instance, firstly, the majority of the patients in the trained group achieved an increase in HR/ST threshold (eight of 12 patients). When changes in HR/ST threshold exceeding the 95 per cent tolerance limit of measurement were considered alone, there was still an increase in HR/ST threshold in five out of the 12 patients. These results confirm, therefore, that the increase in HR/ST threshold after a period of physical training can be shown with patients acting as their own control. Secondly, considering the control group separately, seven of the original 12 patients at entry to the study were judged independently to have deteriorated on clinical grounds. The majority of the remaining patients who were not eliminated by clinical assessment of deterioration ended with a decrease in the HR/ST threshold (four out of five patients). Therefore, when patients in the control group were considered, with the patients acting as their own control, natural progression in the myocardial ischaemia could be detected both by clinical assessment and by using the decrease in HR/ST threshold. Finally, these results were confirmed when statistical analysis of sequential results in the two groups as a whole was used. Thus, in the two groups which were similar in respect of age, sex, and initial disability as determined by exercise testing, a significant increase in HR/ST threshold was achieved in the training group and a significant decrease in the threshold was achieved in the absence of physical training in the control group. Throughout the study, none of the patients in these two groups had been started on beta-blocker or nifedipine therapy.

While it was not the purpose of this study to investigate the mechanism(s) involved in this improvement (an increase in HR/ST threshold), such an improvement can be caused by an increase in myocardial oxygen availability which may be brought about by the development of new collateral vessels, an increase in the capacity of existing collaterals, or by biochemical changes either in the blood or in the myocardium. These considerations stem from previously reported experimental evidence. Thus there is evidence that training in rats and dogs leads to an increase in coronary vascularity, maximum coronary blood flow, and myocardial oxygen consumption.[15 17 37 38] Similarly, significant biochemical alterations were shown to occur in the hearts of rats after training.[14 39 40]

The results of this study, therefore, indicate that such convenient but short physical exercises, known to result in an improvement in the capacity to exercise,[8 10] can effect directly an increase in myocardial oxygen consumption at a given level of myocardial ischaemia in patients with coronary artery disease.

The authors are grateful to the British Heart Foundation and the Wellcome Trust for financial support.

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Br Heart J 1980; **43**: 270–275

Dual isotope stress testing in congenital atresia of left coronary ostium

Applications before and after surgical treatment

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SUMMARY A 38-year-old woman presented with an 11-year history of angina pectoris. Coronary arteriography disclosed a large right coronary artery which filled the entire left coronary tree retrogradely. The left main coronary artery ended blindly and was not connected to the aortic root. There were no atherosclerotic lesions in any vessel. Exercise thallium-201 scintigrams showed a perfusion defect in the anterior region of the left ventricle and exercise first pass radionuclide ventriculography showed anterior hypokinesis of the left ventricle with an ejection fraction of 54 per cent, compared with 60 per cent at rest.

An aortocoronary saphenous vein graft was constructed to the left coronary artery. Four months after operation the patient is free from symptoms. Repeat thallium scintigrams were normal. Exercise radionuclide ventriculography after operation disclosed no wall motion abnormality, and ejection fraction on exercise was 70 per cent.

The mechanism of angina in this patient is unclear but may have been related to the abnormal timing of delivery of blood to the left ventricular myocardium. Dual radionuclide stress testing showed abnormalities of perfusion and wall motion associated with this anomaly, and the reversal of these abnormalities after operation. This non-invasive approach may be useful in the assessment of the physiological significance of coronary anomalies and of the value of corrective surgery.

Single coronary artery and origin of both coronary arteries from the same sinus of Valsalva have generally been regarded as minor congenital abnormalities of little clinical significance.[1] In the absence of associated severe congenital cardiac lesions the anomalies are compatible with longevity.[2]

The widespread use of coronary arteriography has led to the more frequent recognition of these anomalies and an appreciation of their potential clinical significance.[3] There are a number of case reports of sudden death in patients with single coronary artery[4 5] or anomalous aortic origin of the coronaries.[3] In addition, myocardial infarction and angina pectoris have been described in conjunction with certain anomalies.[6 7] Myocardial perfusion scintigraphy with thallium-201 and radionuclide ventriculography have proved valuable in the non-invasive assessment of the physiological changes occurring with stress in patients with atherosclerotic coronary artery disease.[8–11]

In this paper we describe the applications of these techniques in the detection of abnormal physiology in a patient with atresia of the left coronary ostium, and the reversal of the abnormalities after surgical treatment.

Case report

A 38-year-old Caucasian housewife was admitted to hospital complaining of diarrhoea, abdominal pain, malaise, nausea, and vomiting. She had previously attended another hospital 19 years ago with similar complaints and a diagnosis of ulcerative colitis had been made, but she defaulted from follow-up. On systematic inquiry she admitted to anginal chest pain for the past 11 years, and as a child she had frequent 'stitch-like' chest pains on exertion. She

Received for publication 6 July 1979

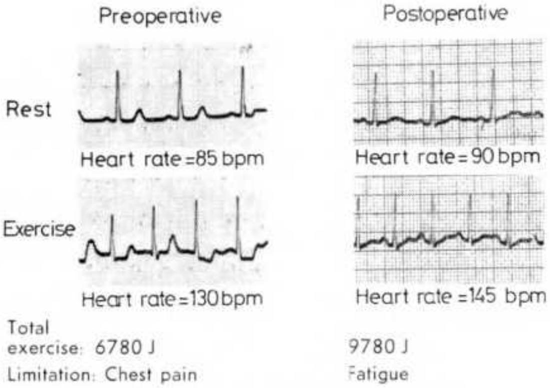

Fig. 1 *Pre- and postoperative rest and exercise electrocardiograms (lead V5). There is ST segment depression and variable T wave alternation during exercise preoperatively which is abolished after surgery.*

had been seen at another hospital 10 years previously with chest pains, and had a positive exercise electrocardiogram. At that time her oral contraceptives were withdrawn and anticoagulant treatment was started. This was discontinued two years later.

On her current admission she was referred to the cardiac department for assessment. On examination she was in sinus rhythm and normotensive. Venous pressure was normal. On auscultation there was a mid-systolic click and late systolic murmur at the apex suggesting prolapse of the posterior cusp of the mitral valve. Electrocardiogram and chest *x*-ray film were within normal limits. An echocardiogram failed to show a systolic prolapse of a mitral cusp. During exercise testing the patient developed chest pain after a total of 6780 joules on the bicycle ergometer. Exercise electrocardiogram (Fig. 1) was positive with 2 mm ST segment depression. In addition, there was variable voltage alternation of the T wave.[12]

At cardiac catheterisation, intracardiac pressures were normal. Left ventricular angiogram was normal with no prolapse of the mitral valve. At coronary arteriography, the left coronary ostium could not be found. The right coronary arteriogram (Fig. 2) showed a large calibre vessel, with the posterior descending artery continuing around the apex and filling the anterior descending directly retrogradely. The remainder of the left coronary tree was opacified via the left anterior descending. The left main stem terminated blindly and was not connected to the aorta. The large apical vessel connecting the posterior descending to the anterior descending is best seen in Fig. 2b.

Simultaneous aortogram and right coronary arteriogram confirmed that there was no connection between aorta and left main coronary. No obstructive lesions of the coronary tree were present.

In an attempt to decide whether this coronary anomaly *per se* could produce abnormal perfusion or wall motion, exercise thallium-201 scintigraphy and exercise first pass radionuclide ventriculography were performed. For stress thallium imaging,

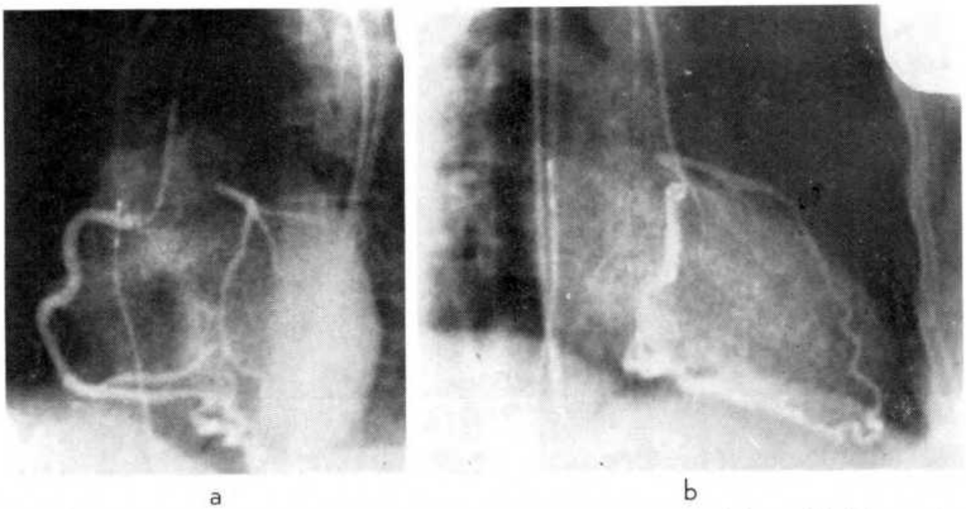

Fig. 2 (a) *Right coronary arteriogram (left oblique projection). The right coronary is large. The left coronary system fills retrogradely over its entire length and the left main ends blindly.* (b) *Right coronary arteriogram (right oblique) which demonstrates a large apical vessel connecting the posterior descending to the anterior descending.*

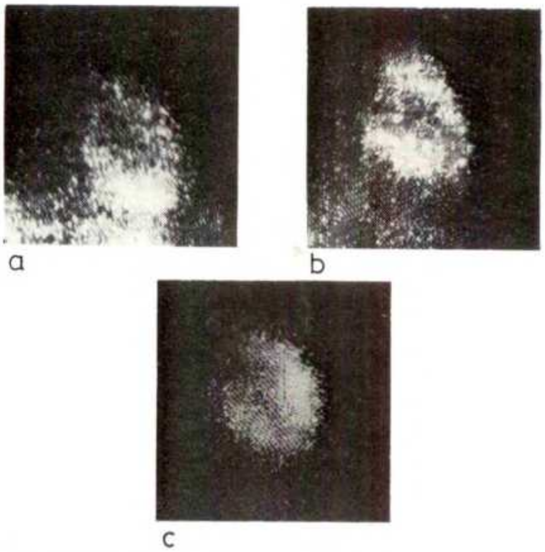

Fig. 3 (a) *Exercise thallium-201 scan preoperatively showing perfusion defect anteriorly.* (b) *Redistribution scan with filling in of the defect. The apical zone shows the normal variant of tracer reduction.* (c) *Exercise scan postoperatively. There is no perfusion defect. All scans are anteroposterior.*

exercise was carried out upright and 2 mCi of the tracer were injected at the onset of angina pectoris. Exercise was continued for a further 60 seconds. Images were obtained with an Ohio nuclear gamma camera and a high resolution parallel-hole collimator, in four standard projections. Five hundred thousand counts per view were collected with a window extending from 65 to 90 KeV (mercury *x*-ray peaks). The camera was linked on-line to a Varian 62OL computer. Images were processed by background correction and analysed according to the criteria of Lenaers *et al.*[13] with perfusion defects regarded as those areas with less than 75 per cent of the maximum intramyocardial counts. Imaging was repeated four hours later at rest, after redistribution of the tracer. Fig. 3a and 3b are anteroposterior images on exercise and at rest. Fig. 3a shows a large perfusion defect anteriorly with normal perfusion inferiorly. At redistribution the defect had disappeared with only some thinning at the apex which is a normal variant.[13]

First pass radionuclide ventriculography was carried out in the right anterior oblique projection using a computerised multicrystal gamma camera (Baird-Atomic, System 77) as previously described.[14] Exercise was supine, and the ventriculograms were performed at angina and after a 20-minute rest period. This technique has been shown to be sensitive for detecting falls in ejection fraction and abnormal wall motion on exercise in patients with obstructive coronary artery lesions.[11] Fig. 4a shows superimposed end-diastolic and end-systolic perimeters from rest (left-hand) and exercise studies, respectively. Ejection fraction measured by count rate changes was 60 per cent at rest and 54 per cent on exercise, with exercise-induced hypokinesis anteriorly.

Fig 4b shows computer derived images of regional ejection fraction, which represent in a 16-colour isocount display the relative contribution of different zones of the left ventricle to ejection

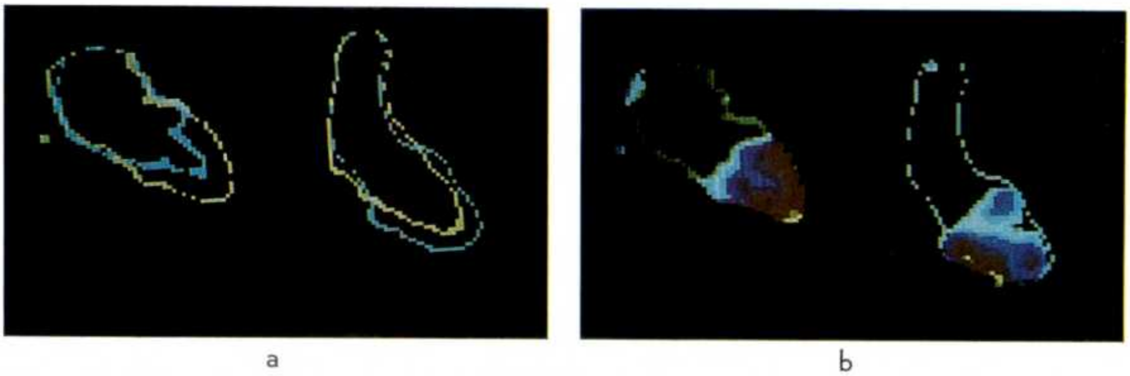

Fig. 4 (a) *Rest (left-hand image) and exercise radionuclide ventriculograms in the right anterior oblique projection. End-diastolic and end-systolic perimeters are shown in each case. Resting ejection fraction = 60 per cent. Exercise ejection fraction = 54 per cent. Anterior hypokinesis develops on exercise.* (b) *Regional ejection fraction images at rest (left-hand image) and exercise. At rest—red and yellow predominate indicating uniform zonal contribution to ejection fraction. At exercise the inferior wall has maximal regional ejection fraction, with the blue, green, and black in the anteroapical region indicating severe reduction in regional function.*

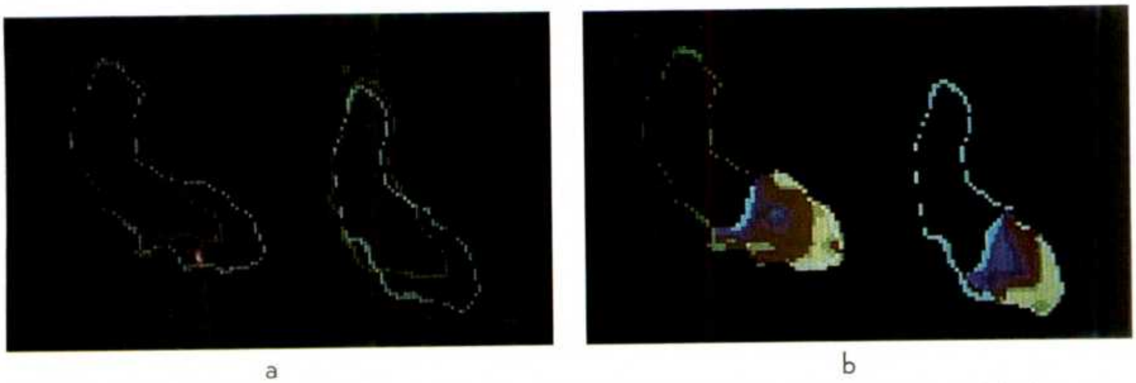

Fig. 5 (a) *Rest (left-hand image) and exercise radionuclide ventriculogram perimeters after operation. Ejection fraction on exercise is 70 per cent, with no hypokinesis.* (b) *Regional ejection fraction images at rest (left-hand image) and exercise postoperatively. Regional ejection fraction at exercise has normalised.*

fraction.[15 16] The end-diastolic perimeter is added in each case. The colour scale ranges from black, which represents the minimum counts per crystal, to yellow, which represents the maximum counts. Thus the left ventricular zones that contribute most to ejection fraction are represented by yellow and red. The resting (left-hand) image of Fig. 4b shows homogeneous contribution to ejection fraction with the yellow and red predominant in all zones. At exercise the inferior wall shows maximal regional ejection fraction but the contribution of the antero-apical segment is poor.

On the basis of these results, the patient was referred for operation, when the right coronary artery was found to be a large vessel situated in the normal position. The distal left anterior descending was abnormally large and tortuous. The aorta was opened to assess the left coronary ostium. There was no left coronary orifice, but a blind dimple in the normal ostial position. An aorto-left anterior descending coronary artery saphenous vein bypass graft was constructed. Postoperative recovery was uneventful.

Two months later the stress testing was repeated. Exercise testing produced fatigue but no chest pain at a heart rate of 145 beats per minute and the exercise electrocardiogram showed no ischaemic changes (Fig. 1). Repeat stress thallium scintigraphy showed no exercise-induced perfusion abnormality (Fig. 3c).

Radionuclide ventriculography was carried out at the point of exercise-induced fatigue. Fig. 5a shows superimposed end-diastolic and end-systolic perimeters at rest (left-hand image) and exercise. No hypokinesis was demonstrable, and ejection fraction on exercise was 70 per cent. Resting ejection fraction was unchanged. Fig. 5b shows the regional ejection fraction images postoperatively; the right-hand image indicates a return to normal of the regional ejection fraction at exercise.

After completion of these investigations, coronary arteriography was repeated. Selective right coronary injection did not result in retrograde filling of the left coronary tree (Fig. 6a) and the large apical connecting vessel shown in Fig. 2 was not visible. The left anterior descending graft was shown to be patent and filled the left coronary system (Fig. 6b). Four months after operation the patient remains free from symptoms.

Discussion

Congenital abnormalities of the coronary arteries are among the rarest of cardiac conditions that may have practical clinical significance. Despite some assertions that coronary anomalies are of only minor importance,[1 2] it has become increasingly evident that a variety of syndromes, from angina pectoris to sudden death, may be associated with abnormal origin of one or more coronary arteries.[4 5 7 17] In many instances symptoms have been attributed to the abnormal course of the aberrant vessel between the aorta and pulmonary artery, or to the acute angulation of the vessel with the aorta so that the coronary orifice is slit-like.[3 17] The case reported here is rare even among the spectrum of coronary anomalies, inasmuch as two normal coronary arterial systems were present. Mullins *et al.*[18] described a 10-year-old child with left coronary ostial atresia and retrograde filling of the left system via collaterals from the right coronary. They drew a distinction between this and the expected anterograde filling of single coronary artery branches. Their patient had clinical and electrocardiographic evidence of myocardial ischaemia with a positive exercise electrocardiogram, which reverted to normal after saphenous vein grafting. Jokl *et al.*[5] described sudden death in a young woman whose entire left ventricular blood supply came from the posterior descending branch of the right coronary, no trace of the left coronary being found. Despite the potentially catastrophic events that can complicate congenital coronary anomalies, the opportunities to study cardiac physiology during stress have been few. Chaitman *et al.*[7] showed abnormal lactate production during pacing and reduced coronary blood flow during exercise in some patients with anomalous origin of the left coronary. Pachinger *et al.*[6] reported deterioration of left ventricular function during pacing-induced angina in another patient.

More recently, thallium-201 perfusion scintigraphy has been applied to the diagnosis of anomalous left coronary artery in the young[19] and in the serial assessment of myocardial perfusion in cases where the left coronary artery arises from the pulmonary artery.[20] This report extends the use of radionuclide techniques to a more unusual coronary anomaly. The defect in anterior perfusion on exercise was coupled with a localised anterior contraction abnormality.

The mechanism of angina in this patient is unclear. One cannot postulate any of the mechanical possibilities previously mentioned such as acute angulation of the coronary with the aorta. It is possible that abnormal timing of delivery of blood to the left coronary territory contributed to angina. The long path taken by blood destined for the left coronary territory may have led to the arrival of the blood in systole, rather than in diastole as is usual. Systolic coronary compression during exercise may have reduced the available blood supply to the anterior wall of the left ventricle to a critical level.[21]

The relief of symptoms after the surgical creation of a two coronary system was given objective support by the postoperative demonstration of disappearance of electrocardiographic, perfusion, and wall motion abnormalities. As in the case of Mullins *et al.*[18] improvement was associated with a patent graft and absence of retrograde flow into the left coronary. Successful surgical correction of other coronary anomalies has been reported[3 22] either by saphenous vein grafting or enlargement of the origin of the anomalous vessel.

It is not known at present whether surgical correction of the type of anomaly described here will be effective in preventing infarction or sudden death in the long term. The reversal of impaired perfusion and abnormal ventricular function under stress is objective evidence that surgical correction is beneficial, and may indicate that direct myocardial revascularisation is the operation of choice in this condition. Stress perfusion scintigraphy and radionuclide ventriculography appear well suited to the non-invasive evaluation of these anomalies.

The authors wish to thank Dr A M Dawson, consultant physician, St. Bartholomew's Hospital, for asking us to study the patient.

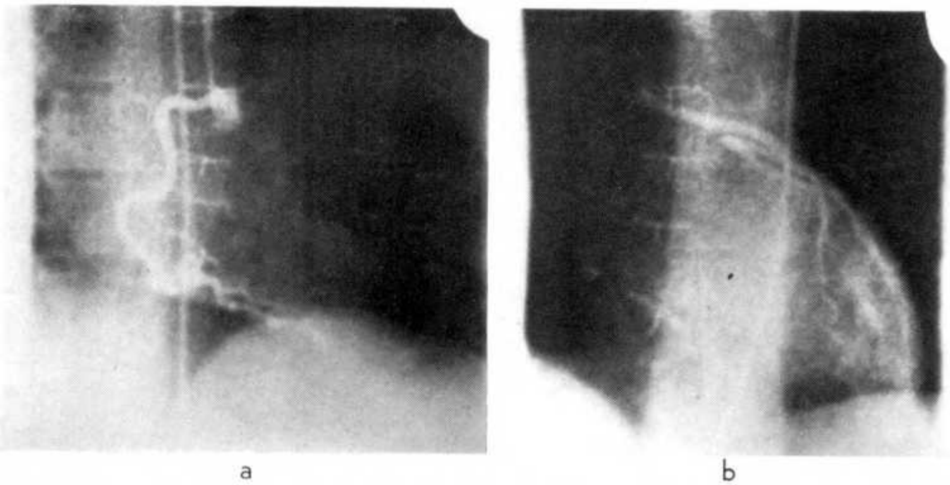

Fig. 6 (a) *Right coronary arteriogram after vein grafting, showing no retrograde filling of the left coronary tree, and absence of the apical connecting vessel.* (b) *Selective injection into the left coronary artery graft. The graft is patent and fills the left anterior descending and circumflex arteries anterogradely.*

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Br Heart J 1980; **43:** 276–283

Non-invasive diagnosis of subpulmonary outflow tract obstruction

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SUMMARY We have studied the echocardiographic and phonocardiographic findings in 18 patients with obstruction to ventricular outflow at subpulmonary valve level. The aetiology was congenital in 13 patients, a result of hypertrophic cardiomyopathy in three, and infiltration of the right ventricular outflow tract by glycogen or lymphoma in the remaining two.

Abnormal systolic motion of the pulmonary valve, fluttering, and early or midsystolic closure were seen in 16 of the 17 patients in whom the cusps were visualised. Normal pulmonary valve motion was found in one patient with coexisting pulmonary valve stenosis. In congenital infundibular stenosis the delay of the pulmonary component of the second heart sound (P2) was related to the severity of the obstruction. A pulmonary ejection sound, defined as a high-frequency sound occurring at the moment of full pulmonary valve opening, was absent except in the patient with coexisting pulmonary valve stenosis. In hypertrophic cardiomyopathy with obstruction to the right ventricular outflow, the ejection systolic murmur was softer with inspiration, a finding that contrasts with the respiratory variation seen with fixed obstruction.

Recognition of these abnormalities should allow an accurate non-invasive diagnosis to be made and permit assessment of severity when P2 can be recorded.

The clinical diagnosis of right ventricular outflow tract obstruction depends upon the recognition of an ejection systolic murmur together with delay of the pulmonary component of the second heart sound (P2). Congenital infundibular stenosis is, however, often associated with other anomalies, particularly ventricular septal defect. The murmur from the ventricular septal defect tends to obscure that from the obstruction to right ventricular outflow, and recognition of the delayed P2 becomes particularly important. In patients with hypertrophic cardiomyopathy, obstruction to right ventricular outflow may occur. This is easily overlooked if clinical assessment has not pointed to the need for careful right ventricular pressure tracings and right ventricular angiography.

Because of the difficulties associated with making the diagnosis of right ventricular outflow tract obstruction at subvalvar level, the present study was undertaken to evaluate the echocardiographic and phonocardiographic findings in 18 patients with this condition. The aetiology of the obstruction was congenital in 13, and the result of hypertrophic cardiomyopathy, glycogen storage disease, or right ventricular tumour in the other five.

Subjects

PATIENTS

Eighteen patients with subvalvar obstruction to right ventricular outflow were studied. Their ages ranged from 3 weeks to 71 years. Twelve of the 18 patients were encountered during routine echocardiographic and phonocardiographic screening before cardiac catheterisation. Six other patients with previously documented right ventricular outflow tract obstruction were identified from the diagnostic indices at St. George's Hospital and North Carolina Memorial Hospital, and were studied retrospectively. The results of cardiac catheterisation and, when available, surgical and pathological findings, are summarised in the Table.

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* Supported by a grant from the Jensen Medical Research Foundation. Present address: The London Hospital, Whitechapel, London E1.

Received for publication 2 July 1979

CONGENITAL INFUNDIBULAR STENOSIS

Cases 1 to 10 had congenital infundibular pulmonary stenosis. In three (cases 1, 2, and 8) this was the only cardiac anomaly, but in the other seven patients (cases 3 to 7, 9, and 10) there was an associated ventricular septal defect. One patient (case 10) had coexisting pulmonary valve stenosis. Of these 10 patients, three (cases 1 to 3) were studied echocardiographically both before and after successful surgical correction. One patient (case 9) had not been studied before operation. After surgical resection of infundibular pulmonary stenosis and closure of a ventricular septal defect, a residual infundibular gradient of 25 mmHg had been found at cardiac catheterisation.

TRANSPOSITION WITH SUBPULMONARY OBSTRUCTION

Two patients (cases 11 and 12) had d-transposition of the great vessels in addition to subpulmonary valve obstruction to left ventricular outflow and one (case 13) had l-transposition.

HYPERTROPHIC CARDIOMYOPATHY

Three patients (cases 14 to 16) had the typical clinical, echocardiographic (septal left ventricular posterior wall ratio greater than 1·5:1), haemodynamic, and angiographic findings of hypertrophic cardiomyopathy. Electrocardiographic abnormalities were similar in all three; there were deep Q waves but positive T wave deflections in leads II, III, and aVF, with similar changes in leads V5 and V7.

All three had undergone cardiac catheterisation (Table). In case 14 there were resting gradients of 60 mmHg across the right ventricular outflow tract and 20 mmHg across the left ventricular outflow tract, these increasing to 100 and 60 mmHg, respectively, on provocation with isoprenaline. At operation, the right ventricular outflow tract was found to be much narrowed by encroachment of the greatly thickened interventricular septum, and part of this was successfully resected leaving no gradient. In case 15 simultaneous right ventricular and pulmonary artery pressures disclosed a gradient of 15 mmHg across the right ventricular outflow tract. There was no gradient across the left ventricular outflow tract at rest or on provocation with isoprenaline or amyl nitrate. Simultaneous left and right ventricular angiograms confirmed the presence of a thickened interventricular septum and the typical angiographic features of hypertrophic cardiomyopathy. In case 16 the haemodynamic findings were similar to those in case 15 (Table).

MYOCARDIAL INFILTRATION

The remaining two patients presented with rare causes of right ventricular outflow tract obstruction. Case 17 was an infant of 3 weeks who presented with respiratory distress and cardiac failure. Chest *x*-ray film showed cardiomegaly and the electrocardiogram showed a short PR interval and biventricular hypertrophy. Echocardiography disclosed prominent asymmetrical septal hypertrophy and systolic anterior motion of the mitral valve. At cardiac catheterisation there was a resting gradient of 25 mmHg across the right ventricular outflow tract, and a gradient of 40 mmHg across the left ventricular outflow tract. Right ventricular angiography showed distinct encroachment of the septum on the right ventricular outflow tract. Surgery was not attempted and the infant's condition deteriorated until he died one week later. At necropsy there were contact lesions on the anterior mitral valve leaflet and the left ventricular aspect of the interventricular septum. The cause of the greatly hypertrophied left and right ventricular free walls and interventricular septum was found to be the result of infiltration by glycogen—Pompe's disease.

Case 18 was a 71-year-old man who presented with a four-week history of increasing weakness and breathlessness. On examination there were large systolic waves in the jugular venous pulse and an ejection systolic murmur was heard at the pulmonary area. The electrocardiogram showed left axis deviation and no evidence of right ventricular hypertrophy; the chest *x*-ray film showed slight cardiomegaly and a prominent left heart border compatible with enlargement of the right ventricular outflow tract. At cardiac catheterisation there was a peak systolic gradient of 55 mmHg between the right ventricle and the pulmonary artery. Right ventricular angiography showed multiple lobular filling defects within the right ventricle. Subsequent necropsy showed that the right ventricular cavity and outflow tract had been invaded by a lymphoma which was responsible for the obstruction to outflow.

Methods

Echocardiograms and phonocardiograms were recorded using either a Smith Kline ultrasonoscope interfaced with a Cambridge multichannel physiological recorder, or an Irex multichannel physiological recorder. High-frequency phonocardiograms from the pulmonary and mitral areas together with the carotid pulse and electrocardiogram were recorded at a paper speed of 100 mm/s. After the recording of the routine echocardiogram, the pulmonary valve echocardiogram was recorded at a paper speed of 100 or 200 mm/s, with appropriate magnification of the echo signal.

Combined tracings of the pulmonary valve echocardiogram and a high-frequency phonocardiogram from the pulmonary area were also recorded. The presence or absence of a pulmonary ejection sound, and correlation of pulmonary valve closure with the pulmonary component of the second heart sound can be accurately assessed from such tracings.

Results

(1) CONGENITAL INFUNDIBULAR PULMONARY STENOSIS (CASES 1 TO 9)

(A) *Echocardiographic findings*

In each patient the echocardiogram showed fine systolic fluttering of the pulmonary valve. This was superimposed on a pattern of either early or mid-systolic cusp closure or coarse chaotic cusp motion throughout systole (Fig. 1). In three patients the posterior pulmonary cusp clearly moved to a 'closed' position in mid-systole (Fig. 2). One patient had low infundibular stenosis caused by abnormal muscle bands ('double chambered right ventricle').[1] The abnormality of pulmonary valve motion in this patient could not be distinguished from that seen in the patients with true infundibular stenosis. The presence or absence of an associated ventricular septal defect did not affect the echocardiographic abnormalities.

In three patients who underwent successful surgical resection of the obstruction, postoperative echocardiographic studies showed normal systolic pulmonary valve motion and increased amplitude of the 'a' dip (Fig. 3). In contrast, systolic fluttering and early closure of the pulmonary valve were demonstrated in the patient who, after resection of infundibular pulmonary stenosis, was shown at cardiac catheterisation to have a residual gradient of 25 mmHg (Fig. 4).

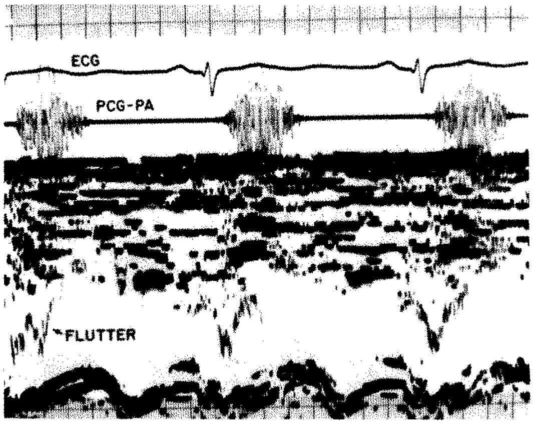

Fig. 1 *Fine fluttering of the pulmonary valve in case 2 with congenital infundibular stenosis. Slight alterations of the transducer angle show different patterns on each cardiac cycle. PCG–PA, phonocardiogram in pulmonary area.*

(B) *Echophonocardiography*

A pulmonary ejection sound, defined as a high-frequency sound coinciding with full pulmonary cusp opening, was not recorded in any of these patients. In three patients, including two in whom P2 could not be recorded, closure of the anterior pulmonary cusp was recorded after the end of the murmur, showing that right ventricular systole was prolonged (Fig. 5).

(C) *Phonocardiographic findings*

The pulmonary component of the second heart sound (P2) was recorded in seven of these nine patients. The degree of delay of P2 relative to A2 during expiration was related to the severity of the obstruction (Table), being 0·09 second with a gradient of 100 mmHg (case 2), and 0·02 second with a gradient of 15 mmHg. The presence of right bundle-branch block accounts for 0·04 second of the delay of P2 in case 9 with a postoperative gradient of 25 mmHg.

(2) CONGENITAL INFUNDIBULAR PULMONARY STENOSIS WITH VALVULAR PULMONARY STENOSIS

In case 10 both infundibular stenosis and pulmonary valve stenosis were present. In contrast to patients with pure infundibular stenosis, systolic motion of the pulmonary valve was normal. In addition a pulmonary ejection sound, softer than that usually found with pure pulmonary valve stenosis, was recorded at the time of full pulmonary cusp opening.

(3) SUBPULMONARY STENOSIS WITH TRANSPOSITION

In three patients (cases 11 to 13) with transposition of the great vessels there was obstruction to left ventricular outflow below the pulmonary valve. In each of these patients the second heart sound was single because of posterior location of the pulmonary valve which rendered the pulmonary component inaudible.

Fluttering of the posterior semilunar (pulmonary) cusps and partial early or mid-systolic valve closure were seen in all three patients (Fig. 6).

(4) HYPERTROPHIC CARDIOMYOPATHY WITH RIGHT VENTRICULAR OUTFLOW TRACT OBSTRUCTION (CASES 14, 15, AND 16)

The pulmonary valve was visualised in two of these three patients, systolic motion showing similar

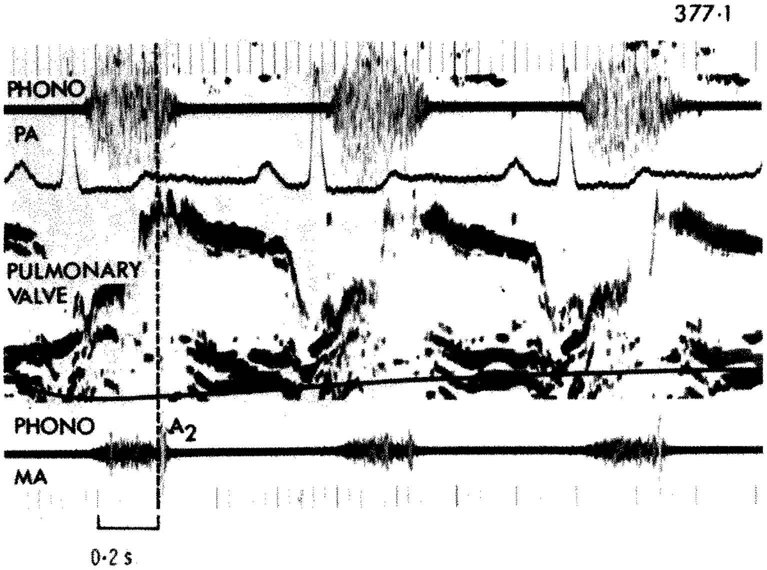

Fig. 2 *Echophonocardiographic study of the pulmonary valve in case 1. The pulmonary valve opens before the QRS on the electrocardiogram. The initial opening motion is a result of the large 'a' wave associated with right atrial hypertrophy. The pulmonary cusp flutters throughout systole and closes midway through the pulmonary ejection systolic murmur. P2 not recorded. Continued vibration can be seen on the pulmonary cusp throughout right ventricular systole, and extending past A2. MA, mitral area.*

abnormalities to those seen in patients with infundibular pulmonary stenosis. In the third patient pulmonary valve motion could not be recorded. In one patient (case 14) who underwent successful myectomy of the right ventricular outflow tract and interventricular septum, pulmonary valve motion returned to normal postoperatively.

Because of the absence of pulmonary artery dilatation in this group the pulmonary valve was difficult to record. The phonocardiographic abnormalities were therefore particularly important. As with congenital infundibular stenosis, P2 was delayed, though the sound was not diminished in intensity. There was no pulmonary ejection sound. The ejection systolic murmur in the pulmonary area increased in expiration and decreased with inspiration, the converse pattern to that found with fixed right ventricular outflow tract obstruction (Fig. 7).

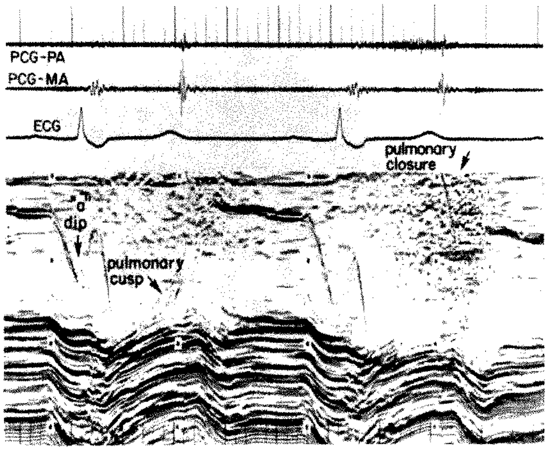

Fig. 3 *Postoperative pulmonary valve echocardiogram from case 3. Pulmonary cusp systolic motion is now normal (best seen in first cardiac cycle). There is no fluttering or early closure of the cusp. The second cardiac cycle shows the closing motion of the anterior pulmonary cusp—a reliable guide to the end of right ventricular systole. This is not delayed in relation to the second heart sound. A large 'a' dip is still present.*

(5) INFILTRATIVE DISORDERS

In case 16, the infant with Pompe's disease, echocardiography identified all the abnormalities simulating hypertrophic cardiomyopathy which were subsequently shown at cardiac catheterisation and necropsy. Apart from showing distinct asymmetrical septal hypertrophy, systolic anterior motion of the mitral valve, and early systolic closure of the aortic valve, echocardiography showed progressive closure and fine fluttering of the pulmonary valve throughout systole (Fig. 8). P2 could not be recorded.

In the patient in whom metastatic lymphoma caused obstruction to the right ventricular outflow echophonocardiographic studies were critical in establishing the presence of prolonged right ventricular systole. These recordings showed a delayed pulmonary component of the second heart sound which clinically had been thought to be a right ventricular third heart sound. The pulmonary valve showed fluttering throughout systole and a reduced opening excursion.

Discussion

The clinical detection of subpulmonary stenosis is often difficult because the systolic murmur may be obscured by that of an associated ventricular septal defect. Even when infundibular stenosis occurs as an isolated lesion, because of the absence of an ejection sound it is more difficult to recognise than pulmonary valve stenosis. The aim of this study, therefore, was to examine the contributions of echocardiography and phonocardiography to the diagnosis and assessment of the severity of this lesion.

The echocardiographic findings of early or mid-systolic closure of the posterior pulmonary cusp, together with fine systolic fluttering, were found to be a sensitive indicator of the presence of subvalvar obstruction. These observations, confirming those of Weyman *et al.*,[2] were made in 15 of the 17 patients in whom the pulmonary valve could be recorded. There were two exceptions; one had co-existing pulmonary valve stenosis, and the thickened and stiff pulmonary cusps were unable to vibrate rapidly. In the patient with lymphoma, the tumour extended up through the valve ring preventing partial closure during systole, and hence only fluttering was seen.

Septal thickening indicating right ventricular hypertrophy was recorded in two patients but otherwise echocardiography was unhelpful in assessing the severity of the obstruction.

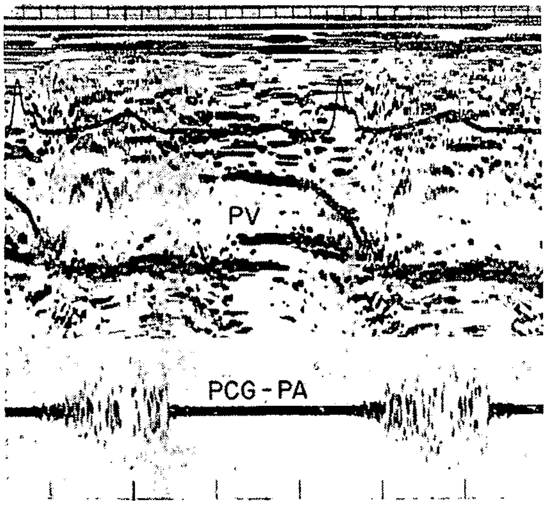

Fig. 4 *Pulmonary valve echocardiogram in a patient with residual infundibular stenosis after operation. The pulmonary valve begins to close at the start of the systolic murmur, and flutters in the closed position during the remainder of systole. PV, pulmonary valve.*

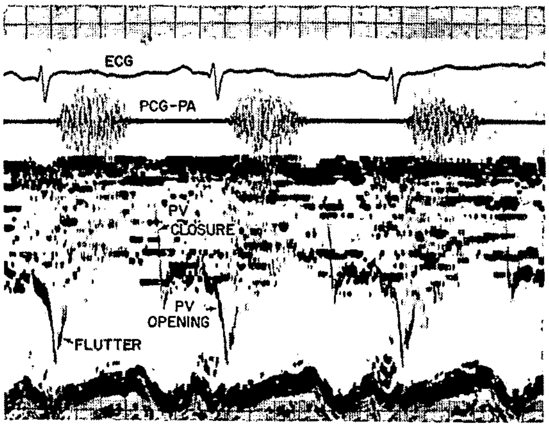

Fig. 5 *Echocardiographic study in case 2 showing pulmonary valve closure occurring well after the end of the ejection systolic murmur. P2 could not be recorded in this patient.*

After successful surgical resection of the stenosis in four patients, pulmonary valve systolic motion returned to normal. In contrast, in the patient shown to have a 25 mmHg residual gradient post-operatively, the typical echocardiographic features of subvalvar obstruction were retained. The delay of P2 was 0·07 second, and allowing 0·04 second for the presence of right bundle-branch block, the 'corrected delay' of 0·03 second correctly suggested that the residual gradient was not severe. Thus echocardiography and phonocardiography provide a useful non-invasive means of assessing the effectiveness of the infundibular resection.

The early or mid-systolic closure of the pulmonary valve seen in infundibular stenosis corresponds with the abnormalities of aortic valve motion reported both in patients with discrete subaortic stenosis[3] and also in hypertrophic cardiomyopathy with left ventricular outflow tract obstruction.[4] In our experience, early systolic aortic cusp closure seen with discrete fibrous subaortic stenosis, and mid-systolic closure in hypertrophic cardiomyopathy, reliably differentiate these two causes of left ventricular outflow tract obstruction. However, in the present series, we were unable to correlate the abnormal pattern of pulmonary valve motion with the cause of subvalvar obstruction. In particular, we found that congenital infundibular stenosis, double chamber right ventricle, and hypertrophic cardiomyopathy could not be distinguished.

The exception to this observation occurred in patients with transposition. Here the cause of the subpulmonary obstruction is usually a typical discrete membrane in the anatomical left ventricle, and the pattern of early systolic closure of the pulmonary valve was the same as that seen in membranous subaortic stenosis (Fig. 6). In one patient the presence of such a membrane just below the pulmonary valve was confirmed at operation. Similar findings have been previously noted in a single case.[5]

It should be emphasised that systolic fluttering of semilunar cusps is a non-specific finding reflecting turbulent flow past the valve. We have seen pronounced systolic fluttering in two patients in whom no gradient could be detected across the infundibulum. One had an atrial septal defect with a left-to-right shunt of 4:1 and the other a cardiac output of 8 l/min. In both cases there was relative obstruction at infundibular level caused by increased flow across a normal outflow tract. In this instance the echocardiographic finding of fine fluttering may be considered as a 'false positive' in terms of predicting an anatomical subvalvar obstruction.

So far we have not encountered this echocardiographic abnormality with a ventricular septal defect, though, theoretically, this could occur if the shunt were sufficiently large. We have not found abnormalities of pulmonary valve motion in Fallot's tetralogy, nor have any been reported.[6, 7] Two factors contribute to this. Technically satisfactory pulmonary valve echocardiograms are usually only obtained from patients with normal or enlarged pulmonary arteries. With infundibular pulmonary stenosis the pulmonary artery at the level of the pulmonary valve is often normal or dilated,[8] whereas in Fallot's tetralogy the pulmonary outflow tract is invariably hypoplastic, often preventing the pulmonary valve being satisfactorily recorded. Secondly, many patients with Fallot's tetralogy have dysplastic or stenotic pulmonary valves which may prevent fluttering of the pulmonary cusps.

There were a number of occasions on which it proved useful to record simultaneous echocardiograms and phonocardiograms. Such tracings allow careful examination of the phonocardiogram at the time of complete pulmonary valve opening, and this is especially important when deciding that the initial vibrations of a systolic murmur do not

Table

Case no.	*Age (y)*	*Diagnosis*	*Confirmation of diagnosis*	*Pressure gradient across outflow tract (mmHg)*	*A2–P2 in expiration*	*Pulmonary valve echo findings*
1	20	Double chamber right ventricle	RV angio, surgery	125	P2 not recorded	Mid-systolic closure and fluttering
2	10	Isolated IPS	RV angio, surgery	100	0·09	Early systolic closure and fluttering
3	25	IPS and VSD	RV angio, surgery	95	0·09	Mid-systolic closure and fluttering
4	8	IPS and VSD	RV angio	80	0·10	Mid-systolic closure and fluttering
5	10	IPS and VSD	RV angio	45	P2 not recorded	Early systolic closure and fluttering
6	23	IPS and VSD	RV angio	50	0·07	Mid-systolic closure and fluttering
7	28	IPS and VSD	RV angio	25	P2 not recorded	Partial closure and fluttering
8	15	Isolated IPS	Pressure gradient alone	15	0·02	Partial closure and fluttering
9	23	Post-op closure VSD and resection RBBB	RV angio	25	0·07	Early systolic closure and fluttering
10	5	IPS and VSD; pulmonary valve stenosis	RV angio	55*	0·07	Normal systolic motion, no fluttering
11	3 wk	ASD and IPS; d-transposition	LV angio	Not measured; LV systolic pressure 75	P2 not recorded	Early systolic closure and fluttering
12	4·5	ASD, VSD, and IPS; d-transposition	LV angio, surgery, necropsy	80	P2 not recorded	Early systolic closure and fluttering
13	27	L-transposition; IPS and VSD	LV angio	100	P2 not recorded	Early systolic closure and fluttering
14	36	HCM R and L; ventricular outflow tract obstruction	RV angio, surgery	60	0·07	Mid-systolic closure and fluttering
15	43	HCM, no resting LV outflow tract obstruction	RV angio	15	0·05	Pulmonary valve not visualised
16	16	HCM, no resting LV outflow obstruction	RV angio	10	0·06	Early systolic closure and fluttering
17	3 wk	Pompe's disease; R and L ventricular outflow tract obstruction	RV angio, necropsy	25	P2 not recorded	Progressive systolic closure and fluttering
18	71	RV outflow obstruction caused by lymphoma	RV angio, necropsy	55	0·11	Pansystolic fluttering

* Gtadient across pulmonary valve 40 mmHg. Gradient across infundibulum 15 mmHg.
IPS, infundibular pulmonary stenosis; VSD, ventricular septal defect; HCM, hypertrophic cardiomyopathy; ASD, atrial septal defect; RV, right ventricle; A2–P2, time interval between the aortic and pulmonary components of the second heart sound measured in seconds; RBBB, right bundle-branch block; RV angio, right ventricular angiogram; LV angio, left ventricular angiogram.

include a soft ejection sound. Using this technique, we found that irrespective of the size of the pulmonary artery, there was no ejection sound in patients with subvalvar obstruction. This confirms the value of this sign in differentiating valvar from subvalvar stenosis, and provides further confirmation of the hypothesis that ejection sounds only originate from abnormal semilunar valve cusps. It should be noted that with severely dysplastic stenotic pulmonary valves the ejection sound may be undectectable.[9]

Echophonocardiography is also of value for studying the end of systole. In two of the three patients with congenital infundibular stenosis in whom P2 could not be recorded, delayed closure of the anterior leaflet of the pulmonary valve provided the only evidence of prolongation of right ventricular systole. Similarly, in case 18 the presence of tricuspid regurgitation in a 71-year-old man suggested that the sound in early diastole was a right ventricular third sound. However, the combined echophonocardiographic study revealed that this was in fact a delayed P2 which, together with the systolic fluttering of the pulmonary cusps, correctly suggested right ventricular outflow tract obstruction. Similar findings have been reported in a patient with a right ventricular myxoma.[10] Finally, the pattern of pulmonary valve motion in primary pulmonary hypertension[11,12] is similar to that seen with infundibular stenosis. The two diagnoses may be distinguished by the phonocardiographic findings in pulmonary hypertension of a loud P2 which is not delayed and the absence of a systolic murmur.

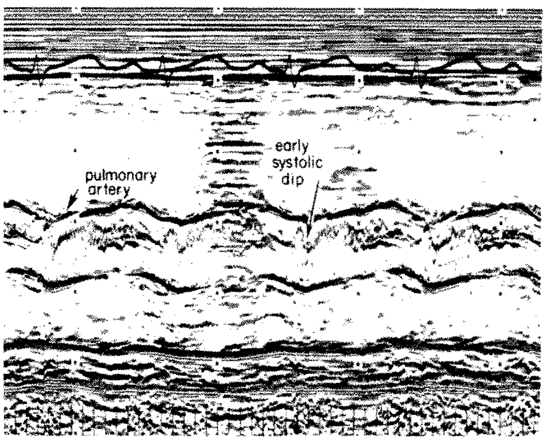

Fig. 6 *Pulmonary valve echocardiogram in case 11 with d-transposition and discrete membranous obstruction to left ventricular outflow. The pattern of early systolic closure and subsequent systolic flutter in the semi-closed position is the same as that seen on the aortic cusps with membranous subaortic stenosis.*

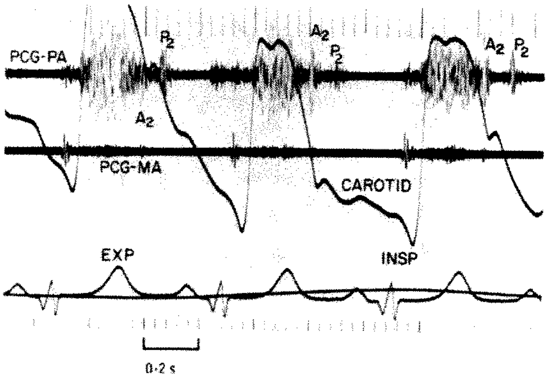

Fig. 7 *Phonocardiogram from case 14. The ejection systolic murmur in the pulmonary area is maximal in expiration and attenuated during inspiration. P2 is loudest in expiration, and is delayed 0·07 seconds after A2. In inspiration P2 is softer and delayed to 0·10 seconds after A2.*

The delay in P2, caused by prolongation of right ventricular systole, is an important diagnostic feature of infundibular stenosis. In addition, we have confirmed the previous observation that phonocardiographic documentation of the delay in P2 provides a useful means of assessing the severity of the obstruction.[13] In the patients with hypertrophic cardiomyopathy, however, the delay in P2 was greater than would be expected from the gradient subsequently documented at cardiac catheterisation. Similar prolongation of right ventricular systole was also shown by the patient (case 18) with florid right ventricular failure resulting from acquired infundibular obstruction. This finding is analogous to reversed splitting of the second sound in aortic stenosis with impaired left ventricular function.

Previous studies have emphasised that the clinical recognition of right ventricular outflow obstruction in hypertrophic cardiomyopathy may be difficult.[14-16] We found that the intensity of the systolic murmur in the pulmonary area was increased during expiration. This variation is the opposite to that seen when the obstruction to outflow is 'fixed', where the murmur is of maximal intensity during inspiration, when there is an increased flow through the right heart. In hypertrophic cardiomyopathy the increase in right ventricular cavity size during inspiration reduces the amount of dynamic obstruction, and hence the intensity of the murmur is diminished during this phase of respiration.

While echocardiography is invaluable for detecting obstruction to left ventricular outflow, the technical difficulty of recording the systolic phase of pulmonary valve motion will tend to limit the value of the technique for detecting right ventricular obstruction in hypertrophic cardiomyopathy. The pulmonary valve was visualised in two of the three adults but this was only after careful searching and the diagnostic features might well remain unrecorded by a 'routine' study. Phonocardiography is, therefore, of particular importance in these patients. In the infant with Pompe's disease simulating hypertrophic cardiomyopathy the pulmonary valve was clearly recorded, showing a pattern typical of infundibular obstruction. In the only other report of a similar case,[17] echocardiographic abnormalities of aortic and mitral valve motion were noted but no comment was made about pulmonary valve motion.

In summary, with subvalvar obstruction to right ventricular outflow there is turbulent blood flow past the pulmonary cusps and prolongation of right ventricular systole. The effects of these alterations of normal physiology may be detected by echocardiography and phonocardiography even in the presence of other cardiac abnormalities.

We thank Drs H Harned, S Schall, R Harrington, A Harris, and Mr J Parker for permission to report patients under their care.

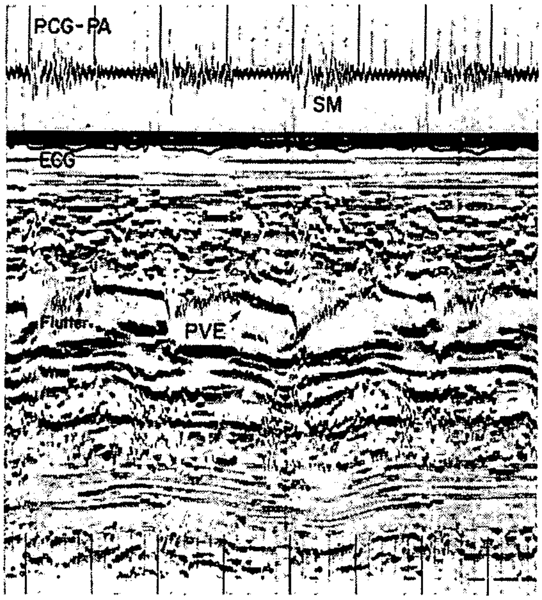

Fig. 8 *Pulmonary valve echocardiogram in case 17. Fluttering and progressive closure of the pulmonary valve can be seen throughout systole. PVE, pulmonary valve echo.*

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Br Heart J 1980; **43**: 284–292

Non-invasive assessment of aortic stenosis by Doppler ultrasound

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SUMMARY The peak pressure drop across the aortic valve in aortic stenosis has been measured by Doppler ultrasound. Maximum velocity in the Doppler signal from the aortic jet was recorded using a maximum frequency estimator. With an angle close to zero between ultrasound beam and maximal velocity in the jet, peak pressure drop can be calculated from the maximal velocity measured; a larger angle will underestimate maximal velocity and pressure drop.

In 57 of 63 patients with aortic stenosis, the aortic jet could be reached by the ultrasound beam and, in 37 of these, peak pressure drop by ultrasound was compared with that obtained at catheterisation.

In patients less than 50 years of age the aortic jet was easy to find, the measurement was reproducible, and underestimation of the pressure drop obtained at catheterisation was within 25 per cent in 17 of 18 patients. In patients over 50 years Doppler signals from the aortic jet were more difficult to obtain, and pressure drop was significantly underestimated in one-third, but time of maximum velocity in systole could indicate whether moderate or severe aortic stenosis was present.

In mitral stenosis it has been shown that maximal velocity in the mitral jet can be measured non-invasively by ultrasonic Doppler technique provided a small enough angle between the ultrasound beam and the mitral jet can be obtained. The pressure drop across the valve can be calculated from the maximal velocity, using the Bernoulli equation, and has been found to correlate well with results obtained simultaneously at catheterisation.[1 2]

In the present study the same method was used to see if the pressure drop across the valve in aortic stenosis could be obtained non-invasively by ultrasound. In 41 patients with aortic stenosis both ultrasound and catheterisation studies were done. In addition, 22 patients with aortic stenosis were studied by ultrasound alone. Among these 63 patients the aortic jet could be recorded by ultrasound in 57.

Theoretical considerations

In a previous study[2] the Bernoulli equation was used to calculate the pressure drop in mitral stenosis from the increase in maximal velocity across the valve, and the following formula was derived:

$$P_1 - P_2 = 4 \times V_2^2 \text{ (mmHg)} \qquad (1)$$

where V_2 = maximal velocity measured in the jet (m/s). The velocity in the left atrium was assumed to be so low that it could be neglected.

An acceleration term originally included in the formula was considered to be of little importance except at valve opening and closure. Viscous losses were also considered, but comparing simultaneous velocity and pressure recordings in mitral stenosis indicated that these terms could be neglected at the velocities present in mitral stenosis.

In this study peak pressure drop across the valve in aortic stenosis was calculated from maximal velocity in the aortic jet measured by Doppler ultrasound using formula (1). The velocity in the left ventricular outflow tract, usually 0·7 to 1 m/s, was neglected. This can be recorded in most patients and becomes important in patients with additional subvalvular obstruction. The maximal velocity of the measured flow (V_2) is obtained from the maximal frequency shift (f_2) of the Doppler

Received for publication 14 May 1979

signal according to the following equation:

$$V_2 = \frac{C}{2f_0} \cdot \frac{f_2}{\cos \theta}$$

where f_0 is the transmitted ultrasonic frequency, C the velocity of sound in blood, and θ the angle between ultrasound beam and the direction of maximal velocity.

To obtain the maximal velocity present in the measured area the angle between ultrasound beam and blood flow must be known or be so small that the cosine of the angle can be approximated to 1 and thus neglected in the equation. With an angle of 20° between ultrasound beam and maximal velocity the velocity will be underestimated by 6 per cent. At a maximal velocity of 2 m/s this will underestimate the pressure drop with 5 per cent and at 4 m/s the underestimation of the pressure drop will be 11 per cent.

The direction of the aortic jet may vary considerably from patient to patient depending on the position of the heart and the aorta and on the aortic valve deformity. With the jet directed mainly upwards the smallest angle would most likely be found from the suprasternal notch or subxiphoid position. With a jet direction more to the right and anteriorly, measurements from the right sternal border—if possible—should give the smallest angle—while with a more posterior direction, aiming from the left sternal border or apex should give the best possibilities. The possible errors with this method therefore include:

Failure to reach the aortic jet.

Failure to obtain a small enough angle between ultrasound beam and maximal velocity.

Failure to maintain an adequate position throughout systole because of movements of the heart and the aorta. Errors introduced by neglecting viscous losses, shown to be unimportant at the velocities present in mitral stenosis.

In this study the ultrasonic and pressure measurements were not done simultaneously except in one case—and changes in cardiac output and peripheral resistance may have resulted in a different peak pressure drop on the two occasions.

Patients and methods

Mean age of the 63 patients was 46 (3 to 89) years. The age of the 41 patients with catheterisation studies varied from 10 to 71 years. Fifteen were less than 20 years, 14 were between 20 and 49 years, 27 patients were between 50 and 69 years, and seven were 70 years or more. Among patients below 20 years 11 were male and four were female, and among those above 20 years 28 were men and 20 women. In 33 patients aortic stenosis was the main valve lesion, 16 had moderate (11) to severe (five) aortic regurgitation, 10 had mitral stenosis, and five moderate to severe mitral regurgitation which, in one, was caused by a ruptured papillary muscle. In one of the 63 patients aortic regurgitation was combined with mitral stenosis.

The pressure drop across the aortic valve was measured by percutaneous retrograde catheterisation via the femoral artery in 35 patients, and by transseptal catheterisation in six. Pressures were recorded with an Elema transducer and an Elema Mingograph. The ultrasonic recording was done one day before catheterisation in most patients, and a few months later in two of the children; the blood pressure, however, was similar on the two occasions.

The apparatus used for the ultrasonic measurements is described in detail elsewhere.[3–5] It can be used in either a pulsed mode when velocities up to 1·75 m/s can be measured, or in a continuous mode when velocities up to 6 m/s can be measured, but with loss of range resolution. To measure the velocities present in aortic stenosis the continuous mode must be used, while the pulsed mode is used to localise the increased velocities to the ascending aorta.

Several positions were tried to record aortic flow, the suprasternal notch, right and left sternal border, apex, and occasionally if these positions failed, the subxiphoid position. When aortic flow was obtained the transducer was moved/angulated to record flow just distal to the aortic valve (in the proximal part of the ascending aorta). In this position a harsh sound of high intensity caused by turbulence can be heard in aortic stenosis. This sound is clearly different from the sound of normal aortic flow. Exploring this area a more high-pitched sound may be recorded when the aortic jet is found. The highest velocity will be recorded in the area with the highest pitched sound. Mean and maximal velocity were then recorded together with the electrocardiogram and phonocardiogram on an Elema Mingograph with paper speed of 25, 50, and 100 mm/s. Peak pressure drop was calculated from the maximal velocity using formula (1).

The time from the start of flow to the peak of maximal velocity was also noted and divided by the duration of flow obtained from the flow curve recorded at 100 mm/s. Only beats where these points were clearly shown were used, and the mean of 5 to 10 beats was analysed. The resulting index ($>0{\cdot}50$ if peak velocity occurred after mid-systole) was compared with the pressure drop. This index was also measured in patients without heart disease and in patients with other valve lesions.

In some patients the ultrasonic examination was repeated on one or more occasions for up to two years.

The patients who were not investigated by methods other than ultrasonic examination were either small children or older patients where surgery was not indicated or was refused.

Results

Doppler signals from the aortic jet were easy to obtain in children and young patients, but at ages above 50 the success rate was much lower (Table 1). In six patients (aged 58 or more) aortic jet velocities could not be recorded, only a harsh sound indicating turbulence and the presence of aortic stenosis. Four of these had significant aortic stenosis and two had moderate stenosis. Doppler signals from the jet were considered inadequate when only weak signals were obtained, or perhaps on only occasional beats or during part of systole. These 14 patients were over 58 years; 12 of them had significant aortic stenosis and two had moderate stenosis.

Table 1 *Doppler signals from the aortic jet obtained non-invasively*

	Good	*Not satisfactory*	*Not obtained*
< 20 years	15	—	—
20–49 years	14	—	—
50–69 years	12	9	6
> 70 years	2	5	—
	43	14	6

The position where the highest velocities were recorded in the 57 patients is given in Table 2, as is the success rate of measuring from the right sternal border. Attempts at recording from the right sternal border were not done in all the patients in the beginning of the study and only in the latter part were the patients turned over to the right side which usually made the recording of aortic jet velocities from this position easier. This may indicate that satisfactory recordings from the right sternal border can be obtained more often than is shown in Table 2.

Table 2 *Positions for best ultrasonic recording of aortic jet velocity*

	No. of patients	
	< 50 years	*> 50 years*
Suprasternal notch	16	13
Right sternal border	10	9
Left sternal border	1	2
Apex	1	4
Subxiphoid position	1	—
	29	28
Aortic jet reached from right sternal border	70%	33%

Fig. 1 shows the maximal velocity curve recorded from the first right intercostal space in one of the patients. Maximal velocity recorded was 4·25 m/s with a calculated peak pressure drop of 69 mmHg. At catheterisation a peak pressure drop of 68 mmHg was found.

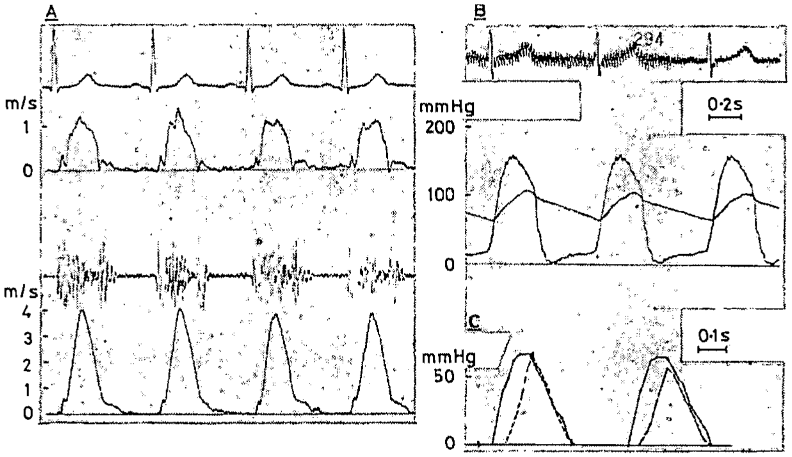

Fig. 1 (A) *Ultrasonic recording of aortic flow from the first right intercostal space, mean and maximal* (below) *velocity;* (B) *pressure recording from the left ventricle and the aorta;* (C) *pressure drop across the aortic valve during systole for two beats.* ——— *by pressure recording,* ------- *by ultrasonic recording.*

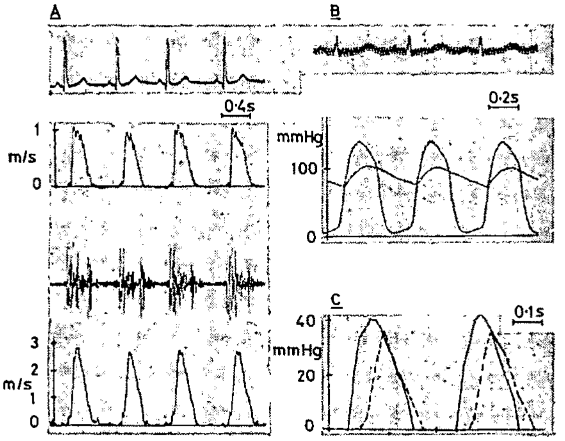

Fig. 2 (A) *Mean* (above) *and maximal velocity of aortic flow measured by ultrasound from first right intercostal space;* (B) *left ventricular and aortic pressure;* (C) *Pressure drop across the aortic valve for two beats.* ———, *pressure recording;* ------, *ultrasonic recording.*

Fig. 2 shows velocity and pressure curves from another patient. Peak pressure drop at catheterisation was 42 mmHg, and maximal velocity recorded was 3·04 m/s with a calculated pressure drop of 37 mmHg. Comparing the pressure drop during systole for the two methods (C), systole was slightly longer during ultrasonic examination when the heart rate was 80 than at catheterisation when the heart rate was 112.

The delay seen in increase in velocity in the first part of systole compared with the pressure tracing was also found when velocity and pressure recordings were done simultaneously (Fig. 3). The maximal velocity curves for the two first beats are regular—giving no reason to suspect failure to record maximal velocities present in the first part of systole. The results in this case indicate that an angle close to zero between the ultrasound beam and maximal velocity was obtained in the first two beats.

The third beat shows an inferior signal but the timing of valve opening and closure is more clearly shown in the lowest curve where the amplitude of the Doppler signal is recorded.

In Fig. 4 the Doppler signal from the aortic jet is recorded simultaneously both with the maximum frequency estimator and a spectral analyser. Peak velocity is not well shown on spectral analysis, but it can be seen that velocities up to 4·5 m/s are present. The maximum frequency estimator gives velocities of 4·90 to 4·97 m/s.

In Fig. 5 peak pressure drop at catheterisation is compared with that obtained by ultrasound in the 37 patients where the aortic jet was found. The pressure drop calculated from the ultrasonic recording was in almost all patients lower than that found at catheterisation.

In eight of the 37 patients the maximal velocity recorded resulted in a significant underestimation of the pressure drop. In seven of these clear signals from the aortic jet were difficult to obtain and made it unlikely that the maximal velocities present were recorded. In the eighth patient, however, flow signals from the jet were easily found and the recorded curves were regular, but maximal velocity and pressure drop were significantly underestimated. At repeat ultrasonic examination after catheterisation higher velocities were not found. In this case

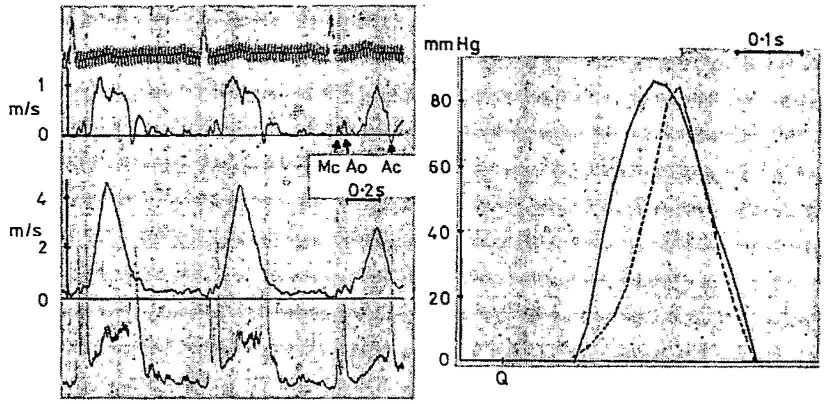

Fig. 3 Right: *pressure drop recorded simultaneously at catheterisation.* ———, *pressure recording;* ------, *ultrasonic recording; Q, start of QRS; Mc, mitral valve closure; Ao, aortic valve opening; Ac, aortic valve closure.*
Left: *ultrasonic recording with mean and maximal velocity and amplitude of Doppler signal (lower curve where timing of valve motions is more clearly seen).*

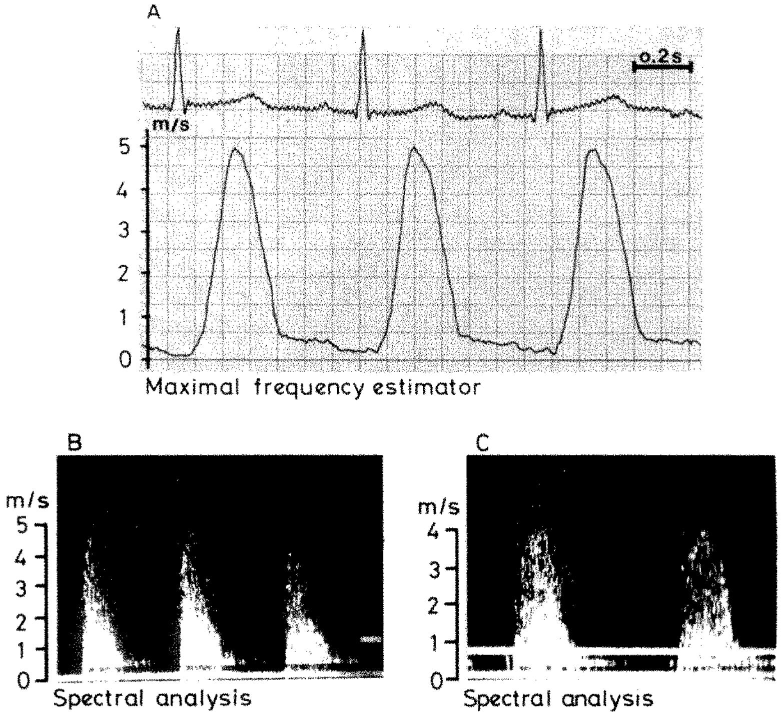

Fig. 4 *Simultaneous recording of Doppler signal from the aortic jet by maximal frequency estimator* (A) *and spectral analyser in one patient* (B). (C) *is from another patient where peak velocity in systole is better seen.*

a small angle to the jet could probably not be obtained.

Fig. 6 is from a patient where Doppler signals from the aortic jet were difficult to obtain. The maximal velocity curve is irregular, indicating that jet velocities are only partly obtained. Maximal velocity recorded was 2·75 m/s with a calculated pressure drop of 30 mmHg. At catheterisation, peak pressure drop across the valve was 130 mmHg. The recording to the left in Fig. 6 was made from the suprasternal notch, and the one in the middle from the left sternal border. In the latter higher velocities were not found, but the maximal velocity curve was more regular allowing the time of peak velocity in systole to be determined. This occurs well after midsystole (0·64). To the right in Fig. 6 flow curves from a normal subject are shown for comparison, with velocity about 1 m/s and peak of maximal velocity early in systole.

In Fig. 7 the time of peak velocity in systole is related to the peak pressure drop at catheterisation. With increasing pressure drop peak velocity was usually found later in systole. It is seen that when peak velocity was later than midsystole (>0·50) pressure drop was more than 50 mmHg in almost all patients. The one exception with lower pressure drop and late peak velocity had severe mitral regurgitation with a short systole.

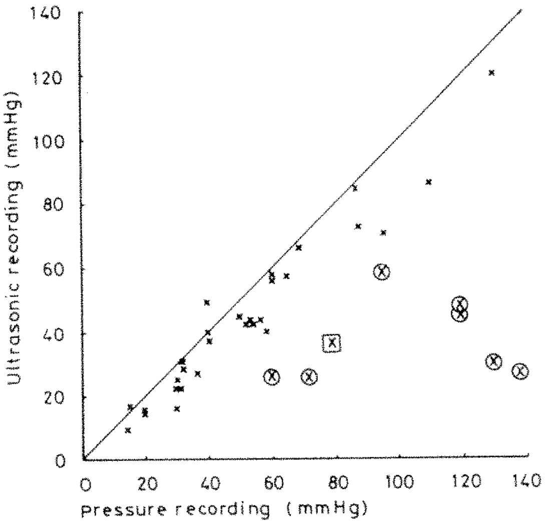

Fig. 5 *Pressure drop obtained by ultrasound compared with pressure drop at catheterisation. In cases marked with a ring auditory signals from the aortic jet were difficult to obtain and the flow curves inadequate. In the one marked with a square the aortic jet was easily found—still significant underestimation of the pressure drop occurred.*

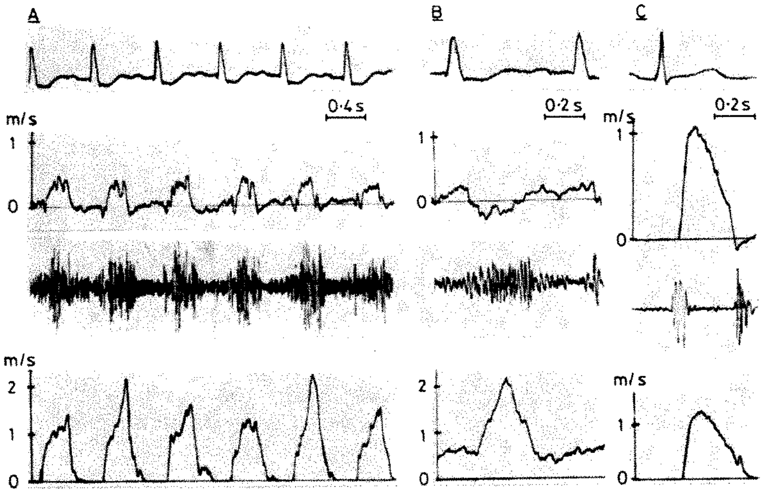

Fig. 6 *Mean* (above) *and maximal velocity recorded from the suprasternal notch* (A), *from the fourth left intercostal space in the same patient* (B), *and in a normal subject* (C).

It is seen that peak velocity was late in systole in seven of the eight patients where maximal velocity was greatly underestimated. This may, therefore, indicate the presence of significant stenosis in these patients and that maximal velocity had not been obtained. The patient (marked with a square on the Figure) was the only one where peak velocity before midsystole was associated with a peak pressure drop greater than 50 mmHg; this patient also had massive aortic regurgitation.

The aortic jet was much easier to find in the young patient and the results were much better. The youngest patient whose pressure drop recorded by ultrasound was much lower than the actual drop was 45 years old (marked by a square in Fig. 5); the other patients where the maximal velocity recorded significantly underestimated the pressure drop were 58 to 70 years.

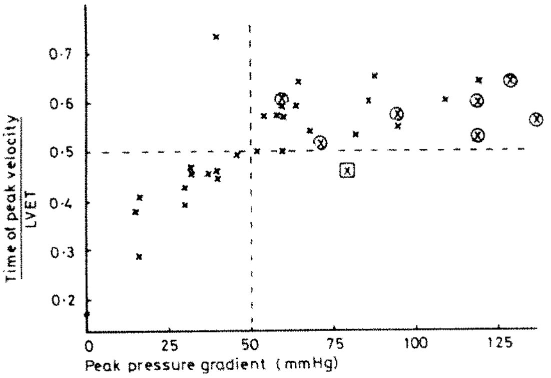

Fig. 7 *Time of peak velocity in systole related to peak pressure gradient at catheterisation.*
LVET, left ventricular ejection time.
The cases marked with rings or a square are the same as those in Fig. 5.

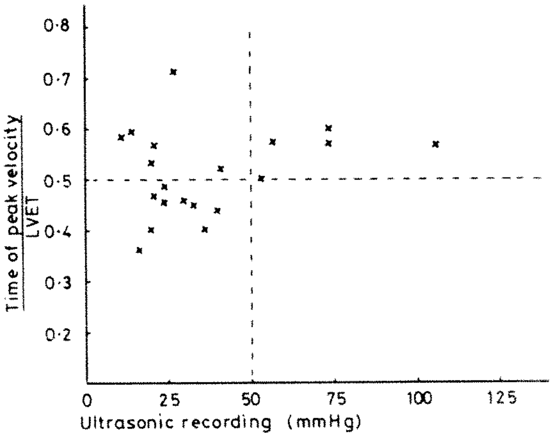

Fig. 8 *Peak pressure drop from ultrasound in the patients without catheterisation related to time of peak velocity in systole.*

Fig. 8 shows the peak pressure drop obtained by ultrasound in 21 of the patients without a catheterisation study and related to the time of peak velocity in systole. The same relation as in Fig. 7 is found. In five of the patients with small pressure drop and late peak velocity, clear Doppler signals from the aortic jet were difficult to obtain and maximal velocity was probably much underestimated. In one of them (peak velocity at 0·71) the presence of severe aortic stenosis was confirmed at operation. The patients with latest peak velocity had additional severe mitral regurgitation.

In patients without heart diseease and in patients

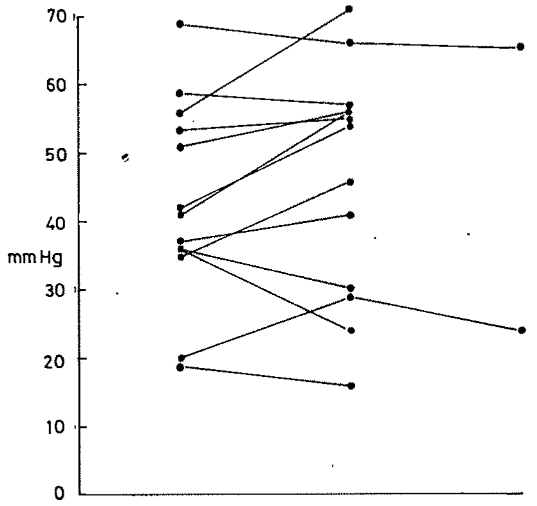

Fig. 9 *Repeat examination in 13 patients. Time between first and second examination three to 15 months (mean 12·4).*

with other heart diseases peak velocity in the ascending aorta occurred earlier except when left ventricular failure or severe mitral regurgitation was present.

In 40 children aged 1 to 20 years (mean 11) the time of peak maximal velocity was found at 0·30 (range 0·22 to 0·37) and was similar in 20 adults (range 0·21 to 0·35). The lowest values were seen in patients with hyperkinetic heart syndrome or with considerable aortic regurgitation (but without heart failure). With left ventricular failure peak velocity occurred later (0·38 to 0·41) and when mitral regurgitation was large enough to shorten left ventricular systole the peak velocity occurred much later (0·38 to 0·52).

Fig. 9 shows the results of repeat studies in 13 patients aged 3 to 29 years. The interval between two studies was usually a year. There was no significant difference between the first and second examination. In patients where adequate signals from the aortic jet could not be obtained, results were not improved at repeat examinations, indicating anatomical reasons for the failure.

When recording from the left sternal border or apex, aortic flow is directed away from the transducer. In these positions the jet of mitral regurgitation may be very close and in nearly the same direction. In mitral regurgitation even higher velocity may be present, especially in patients with high systolic pressure in the left ventricle where the pressure difference between the ventricle and atrium is large. In two of the patients with mitral regurgitation these high velocities were found in the blood flow back into the left atrium in addition to the high velocities in the aortic jet found in a slightly superior direction when recorded from the apex. Using pulsed ultrasound the high velocities could be located behind the mitral and aortic valves, respectively, in both cases. Flow in mitral regurgi-

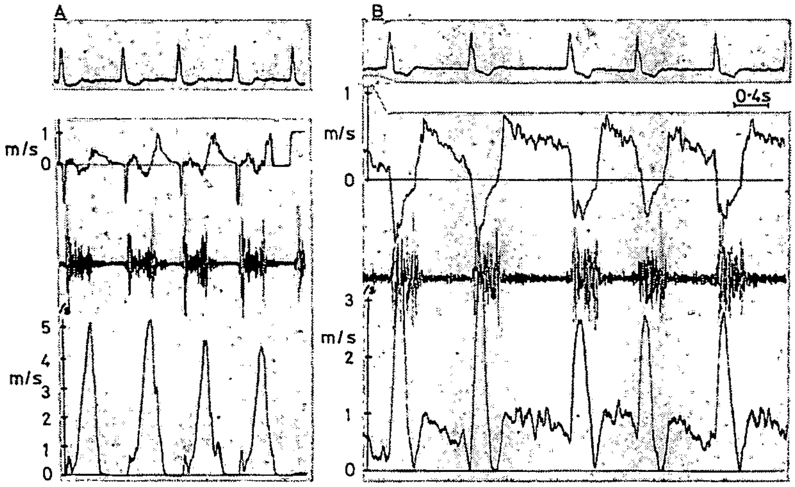

Fig. 10 *Mean and maximal velocity curves recorded from the apex (with continuous ultrasound). Mean velocity is directive, flow towards the transducer is positive, and flow away from the transducer is negative. Maximal velocity is non-directive. (A) Aortic stenosis: mitral valve closure away from the transducer is also seen and in diastole some mitral flow; (B) mitral regurgitation. Flow is away from the transducer in systole with start of flow at mitral valve closure. In diastole flow into the left ventricle is recorded.*

tation also started earlier, at the closure of the mitral valve and maximal velocity was reached shortly after, compared with the later start of flow and later peak of maximal velocity in the aorta as shown in Fig. 10. Fig. 11 is redrawn from the angiogram showing the small angle between the aortic jet and mitral regurgitation in one of these. In the other cases of mitral regurgitation, flow also started at the closure of the mitral valve but lower and rather unchanged velocities during systole were found.

Discussion

The results in the patient with simultaneous ultrasonic and pressure recording, with a peak pressure drop of 84 and 86 mmHg, respectively, indicate that the applied formula can be used to calculate peak pressure drop from maximal velocity at the velocities present in aortic stenosis.

The delayed increase in velocity compared with the pressure recording is probably a result of the omission of a second acceleration term in the formula. As discussed in a previous paper,[2] only convective acceleration is considered in the formula while acceleration resulting from changes in velocity with time was found to be of importance at the time of valve opening and during increase in velocity. At peak velocity this term could be ignored, and in mitral stenosis the period at the beginning of diastole where this term was of importance was so short that it could be ignored also in calculating mean pressure drop. That this delay is more evident in aortic stenosis may possibly be because of the longer acceleration period and the higher velocities. A possible delay caused by the frequency response of the maximal velocity estimator is calculated to be within five milliseconds and cannot fully explain the delay in the maximal velocity curve. Another possibility is that viscous losses may be of significance in aortic stenosis. This delay must be considered in the estimation of mean pressure drop in aortic stenosis but does not influence the calculation of peak pressure drop.

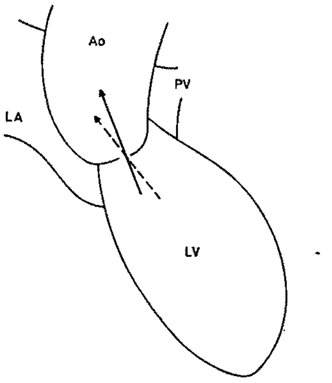

Fig. 11 *Redrawn from the left ventricular angiogram from a patient with aortic stenosis and mitral regurgitation.*
LA, left atrium; LV, left ventricle; PV, pulmonary vein; Ao, aorta. Solid arrows indicate aortic jet and stippled arrow indicates mitral jet.

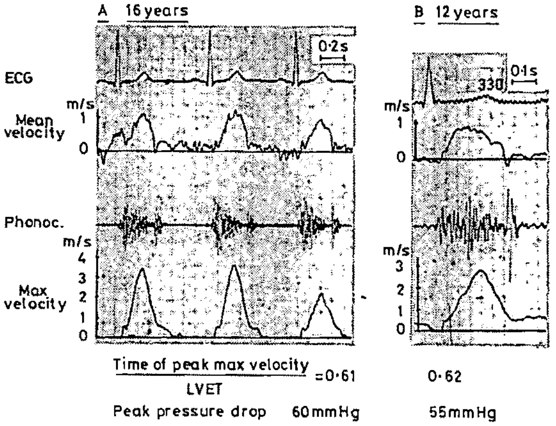

Fig. 12 *Maximal velocity from the aortic jet shows peak velocity after mid-systole in both patients, and later in systole than peak murmur. Peak pressure drop at catheterisation is noted below.*

To obtain maximal velocity in the aortic jet non-invasively by ultrasound, the jet must be reached by the ultrasound beam and with a small angle between these to get a good estimate of the maximal velocity present in the jet. If the aortic jet is not reached no quantification of the pressure drop is possible, but a harsh sound of turbulence may still indicate the presence of aortic valve stenosis. Such a Doppler signal, instead of the more tone-like signal from normal aortic blood flow, has been reported as a reliable sign of aortic valve stenosis,[6] and was present in all patients in this study, including those where signals from the aortic jet could not be obtained. If the aortic jet can be reached but with a substantial angle to the ultrasound beam maximal velocity and the pressure drop will be underestimated.

The difference in success rate with age both in finding the jet, obtaining good Doppler signals and good correlation to pressure may have anatomical reasons. With age, emphysema may limit the access to the ascending aorta, and increased valve deformity and calcification may produce greater variations in jet direction in the older patients.

Below 50 years good Doppler signals were easily obtained in all, and peak pressure drop was significantly underestimated in only one of 18. In the age group above 50 years satisfactory results were obtained in only 40 per cent, but time of peak maximal velocity in systole indicated whether mild or severe aortic stenosis was present in the 82 per cent where signals from the jet were obtained. The possibility must be considered that significant aortic regurgitation will cause peak maximal velocity to occur relatively early in systole; and that mitral regurgitation or left ventricular failure may result in it being relatively delayed.

In this study peak maximal velocity after mid-ejection was almost always associated with a peak pressure drop above 50 mmHg. This may be compared with the timing of the maximal intensity of the systolic murmur, a late peak of murmur indicating a more severe stenosis.[7] [8] In children, the peak of the murmur may be unreliable with an early peak despite a high pressure drop.[9] In the children in the present study peak velocity was found at or after mid-systole when peak pressure drop was above 50 mmHg, even if the peak of the murmur occurred earlier (Fig. 12).

In an effort to avoid underestimation of the pressure drop, several transducer positions should be tried and the region where the jet is found must be carefully scanned to obtain the best possible angle to the jet. When measurements are made from the apex or left sternal border care must be taken to distinguish between the jet of mitral regurgitation and the aortic jet. Subvalvular aortic stenosis can also be distinguished as the high velocity can then be localised to the left ventricular outflow tract below the aortic valve using pulsed ultrasound from the apical region.

Repeat measurements did not indicate any significant change in pressure drop over one to two years. This also indicates the reproducibility of the method, which may help in the non-invasive assessment of aortic stenosis provided the possibility of underestimating the pressure drop is kept in mind. It seems especially useful in children and young patients and in the follow-up of all patients where the jet is easily found.

This work was supported by the Norwegian Council on Cardiovascular Disease.

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Br Heart J 1980; **43**: 293–300

Effects of propranolol on left ventricular wall movement in patients with ischaemic heart disease

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SUMMARY To assess the acute and chronic effects of propranolol on left ventricular wall motion, simultaneous echo-, apex-, and phonocardiograms were recorded in 10 normal subjects and in 16 patients with ischaemic heart disease, nine with co-ordinate (group A) and seven with incoordinate (group B) contraction in the control state. Records were made after 0·1 mg/kg intravenous or oral therapeutic dose for one week. In all, propranolol caused small reductions in heart rate and peak VCF. In normal subjects, intravenous and oral propranolol caused rate-related increases in the intervals Q to A2, Q to minimum dimension, and Q to mitral valve opening. The effects were different in patients with ischaemic heart disease. In group A, inward wall movement ceased 80 ms early, and this was not attributable to a change in heart rate. Diastolic events were unaltered. In group B, minimum dimension already occurred early. Propranolol did not alter systolic events further, but increased delay in mitral valve opening, 'O' point, prolonged isovolumic relaxation, reduced peak rate of dimension increase, and aggravated incoordinate relaxation. It is concluded that the effects of propranolol in patients with ischaemic heart disease are modified in a manner that cannot be predicted from observations made in normal subjects. It also appears that complex drug effects can be assessed in man from the measurement of time intervals derived from multiple non-invasive techniques.

Propranolol is often used to treat patients with coronary artery disease. Though its haemodynamic effects have been studied,[1 2] information about its action on incoordinate left ventricular wall movement is contradictory: dyskinesis having been reported as increased,[3] unchanged,[4] or improved[5] by the drug. These discordant results might reflect the rather unsatisfactory nature of angiography as a means of studying drug action. We have therefore used echocardiography to investigate the effects of acute intravenous and chronic oral administration of propranolol in patients with coronary artery disease, with particular reference to assessing disturbances in the velocity and timing of left ventricular wall movement, rather than attempting to measure small changes in its extent.

Patients

Observations were made on 16 patients with angina pectoris (15 men and one woman, mean age 49 ±3 years), in whom the diagnosis of ischaemic heart disease had been established by cardiac catheterisation and coronary arteriography at King's College Hospital. The patients all consented to take part in the study, having had full information about its nature and purpose. They were in sinus rhythm, and none had mitral or aortic regurgitation. Ten normal subjects, matched for age, sex, and oral propranolol dose were also studied, using an identical precedure.

Oral beta-blocking drugs were discontinued three days before the study. Echocardiograms with simultaneous phono- and apexcardiograms were obtained from each subject in a control resting state. In the acute study, observations were repeated 25 minutes after 0·1 mg/kg propranolol had been given intravenously. In the chronic study, the patients restarted their individual antianginal dose of oral propranolol (120 to 240 mg/day), and were reinvestigated after one week. Arterial blood pressure was recorded by sphygmomanometer on each occasion, after the echocardiogram had been performed.

Methods

Echocardiograms were recorded with a Smith-Kline Ekoline 20 ultrasonoscope, using a 2·25 MHz

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Received for publication 10 October 1979

transducer, with the patients in the left semilateral position. Echocardiograms were only accepted for analysis if they showed the time of separation of the mitral valve leaflets, and clear, continuous endocardial echoes from the posterior left ventricular wall and the left side of the septum throughout the cardiac cycle. Phonocardiograms were recorded from the position on the praecordium where splitting of the second sound was most obvious clinically, using a Leatham suction microphone and a high-frequency filter. Apexcardiograms were recorded from the position of maximum impulse. A Cambridge Scientific Instruments transducer was used with a 3 cm cup, a time constant of 4 s, and a lower frequency limit of 0·05 Hz. Echo-, apex-, and phonocardiograms were recorded simultaneously using a Cambridge photographic recorder at a paper speed of 100 mm/s (Fig. 1).

The echocardiograms were digitised[6] on a Summagraphics digitiser and processed by a Prime 300 computer system. Co-ordinates were generated from septal and posterior endocardial echoes and from the apexcardiogram, and records were calibrated by points defining 1 cm depth, 500 ms time, and two successive Q waves of the cardiac cycle in question. The timing of A2, the onset of the first high frequency vibration of the aortic component of the second sound, and of mitral valve opening, taken as the initial separation of the mitral valve cusps at the start of filling, were also superimposed on records. At each step of the investigation, two cardiac cycles were digitised and mean values used. Continuous plots over one cardiac cycle were obtained, showing original digitised data, left ventricular cavity dimension, its rate of change both in cm/s and normalised to refer to unit length of dimension, and the loop of dimension against apexcardiogram.[7] From these plots, the following measurements were made:

(1) *Time intervals:* (a) Cycle length as the interval between successive Q waves: the onset of the first Q wave was always taken as zero time; (b) Q to aortic valve closure (A2); (c) Q to the onset of mitral valve opening (MVO); (d) Q to the 'O' point of the apex cardiogram; (e) Q to the time of minimum left ventricular dimension, the point in late systole when the first derivative of cavity dimension first changed from negative to positive; (f) Q to the time of peak rate of dimension increase during diastole; (g) Q to left ventricular dimension discontinuity, taken as

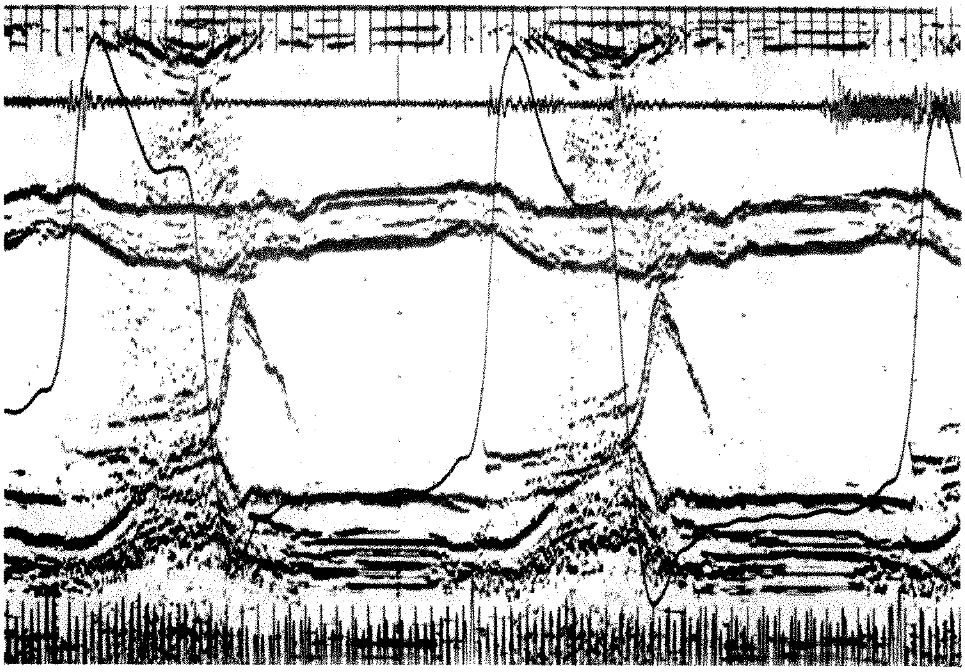

Fig. 1 *Echocardiogram of left ventricular cavity from a patient with ischaemic heart disease, with simultaneous apex-, phono-, and electrocardiogram. Paper speed 100 mm/s.*

Table 1 *Correlation coefficients for cycle length*

	Q wave to							*Isovolumic relaxation time*	*Aortic closure to 'O' point*
	Aortic closure	*Mitral opening*	*'O' point*	*LV discontinuity*	*Peak filling*	*Minimum dimension*			
						A	*B*		
Control	0·82	0·75	0·69	0·71	0·78	0·75	0·79	−0·29	0·23
Intravenous propranolol	0·79	0·79	0·69	0·75	0·77	0·25	0·76	−0·13	0·22
Oral propranolol	0·63	0·63	0·56	0·48	0·58	0·20	0·68	−0·34	0·46

32 degrees of freedom.

the time at which the rate of dimension increase drops abruptly to 20 per cent of less of its peak value.

(2) *Changes of LV dimension during following periods:* (a) The time of inscription of the upstroke of the apexcardiogram, measured from the loop; (b) isovolumic relaxation, taken as the interval A2 to MVO; (c) the time of inscription of the downstroke of the apexcardiogram, measured from the loop.

(3) *Normalised peak rates of dimension change:* (a) During ejection (peak VCF); (b) during diastole.

(4) *Maximum and minimum left ventricular dimensions.*

The patients with ischaemic heart disease were initially considered as a single group, and were then divided according to the timing of minimum cavity dimension with respect to A2. In normal subjects, A2 precedes minimum cavity dimension by 40 ±10 ms (mean ±1 standard deviation),[8] but if abnormalities of isovolumic contraction are present then minimum cavity dimension follows A2 by less than 20 ms, the 95 per cent confidence limit of normal. Group A patients (synchronous contraction) were thus taken as those with ischaemic heart disease in whom A2 preceded minimum dimension by 20 ms or more, and group B (asynchronous contraction) as those in whom separation was less.

Statistical significances of differences between mean values were examined by an analysis of variance. Linear regression analysis was used to measure correlation between variables. Mean values for time intervals were all expressed to the nearest 5 ms.

These are given in detail in Tables 1 and 2 and Fig. 2 to 4.

NORMAL SUBJECTS

In normal subjects, intravenous propranolol caused

Table 2 *Effect of oral and intravenous propranolol in ischaemic heart disease*

	Group A (n=9)			*Group B (n=7)*			
		Propranolol			*Propranolol*		
	Control	*Intravenous*	*Oral*	*Control*	*Intravenous*	*Oral*	*SE*
RR interval (ms)	910	1045	1000	840	975	1050	30
Q to:							
A2 (ms)	385	415	390	380	390*	+410	9
Minimum dimension (ms)	450	450	++400	355***	370***	390	29
Mitral opening (ms)	465	+490	470	445	++485	++500	11
Peak filling (ms)	520	535	515	475*	510	510	24
'O' point (ms)	525	550	520	480**	++530	++545	15
Discontinuity (ms)	640	670	630	600	630	++685	45
QS2 index (ms)	530	540	520	540	530	535	8
Isovolumic relaxation (ms)	80	75	80	65	+++ 95*	++ 85	12
A2 to 'O' point (ms)	140	130	130	100**	++140	+140	14
Minimum D − A2	65	+ 35	+ 15	−25***	−15*	−20	29
MVO − minimum dimension (ms)	15	++ 45	++ 65	90***	115***	110*	29
Dimension change (upstroke, %)	−3	−3	−8	−14**	−12*	−21**	6
Dimension change (IVR, %)	−5	0	++ 8	16***	28***	23**	6
Dimension change (downstroke)	28	33	38	34	44	50	9
Peak VCF (s^{-1})	2·5	2·2	2·5	2·9	2·5	2·5	0·53
Peak diastolic dimension increase (s^{-1})	3·6	++ 3·0	3·4	3·8	3·1	3·1	0·61

Statistical significances: + refers to differences between control and oral or intravenous propranolol (+, $p < 0·05$; ++, $p < 0·01$; +++, $p < 0·001$). * refers to differences between groups A and B for corresponding values (*, $p < 0·05$; **, $p < 0·01$; ***, $p < 0·001$). MVO, mitral valve opening; discontinuity, discontinuity on first differential trace; SE, standard error.

an increase in RR interval from 845 to 1005 ms ($p<0{\cdot}001$). There was also prolongation of the interval from the Q wave of the electrocardiogram to aortic valve closure from 370 to 400 ms ($p<0{\cdot}01$), Q to minimum dimension from 420 to 455 ms ($p<0{\cdot}05$), and Q to mitral valve opening from 450 to 475 ms ($p<0{\cdot}01$). Peak rate of dimension change during systole and diastole remained unaltered, as did the intervals aortic valve closure to minimum dimension, minimum dimension to mitral valve opening and isovolumic relaxation. The timing of the 'O' point of the apexcardiogram and of peak filling were also unaffected. Changes after oral propranolol were in a similar direction, though they were not statistically significant. Neither oral nor intravenous administration of propranolol caused any significant change in arterial pressure. However, a small reduction in peak VCF from 2·5 to 2·1 s^{-1} was noted ($p<0{\cdot}05$) after oral propranolol.

The increase in QA2 interval after intravenous propranolol appeared to be directly explicable on the basis of the reduction in heart rate, since there was no significant change in QS2 index.[9] The effect of spontaneous variation in heart rate on the interval Q-minimum dimension was investigated in 34 additional normal subjects, and positive correlation demonstrated with RR interval, the regression equation being:

Q-min D = 0·29RR + 170 ms, r = 0·86, $p<0{\cdot}001$.
Standard error of the estimate, 23 ms.

(Fig. 2). The increase in Q-minimum dimension interval brought about by intravenous propranolol in normal subjects was thus entirely explicable on the basis of the drop in heart rate.

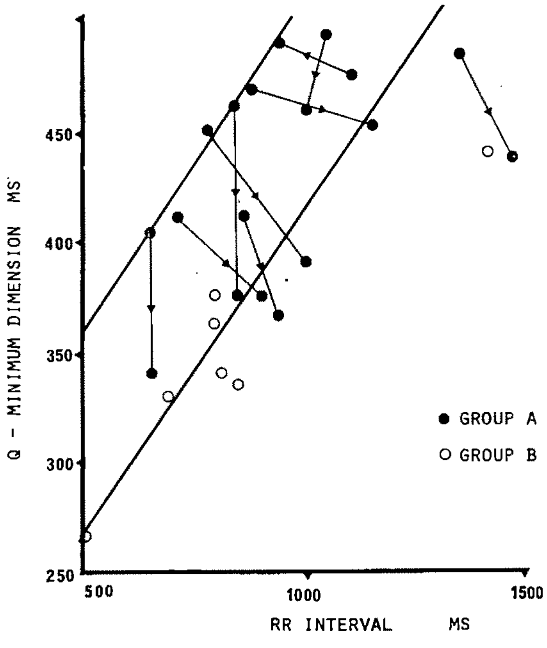

Fig. 2 *Relation between changes in the interval Q to minimum dimension and RR interval. The limits represent two standard deviations about the regression line derived from normal subjects. Values for group A patients are shown before and after oral propranolol administration, with the arrow pointing to the latter values.*

ISCHAEMIC HEART DISEASE

In the patients with ischaemic heart disease, propranolol caused a significant increase in RR interval of 130 ms after both oral and intravenous administration ($p<0{\cdot}001$ for each). This reduction in heart rate was associated with an increase in QA2 interval of 26 ms ($p<0{\cdot}001$), though when corrected for rate, and expressed as a QS2 index,[9] it was unchanged. There were also small associated changes in the intervals Q to mitral valve opening by 30 ms ($p<0{\cdot}001$ after intravenous, and $p<0{\cdot}05$ after oral propranolol), and in isovolumic relaxation time by 10 ms ($p<0{\cdot}01$). Maximum and minimum cavity dimensions were unchanged, but the mean reduction in dimension during systole dropped from 1·8 to 1·6 cm ($p<0{\cdot}05$). Peak VCF dropped from 2·7 to 2·3 s^{-1} ($p<0{\cdot}05$), and peak rate of dimension increase during filling from 3·7 to 3·1 s^{-1} ($p<0{\cdot}01$). During oral propranolol administration, there were changes in the pattern of wall movement. Incoordinate contraction became apparent, with a 14 per cent ($p<0{\cdot}05$) reduction in dimension during the time of inscription of the upstroke of the apexcardiogram (normal, up to 14%). There was also evidence of abnormal relaxation, with an increase in dimension of 41 per cent during the downstroke of the apexcardiogram ($p<0{\cdot}05$, normal up to 33%). Neither oral nor intravenous propranolol administration caused any significant change in blood pressure.

Effect of heart rate

In view of the drop in heart rate caused by propranolol administration, regression equations relating the RR interval to other variables were derived, based on spontaneous variation in rate. Under control conditions, there was significant positive correlation between RR interval and the intervals from Q wave to minimum dimension in both group A and group B, to A2, mitral valve opening, 'O' point, timing of peak rate dimension increase, and the end of rapid filling ($p<0{\cdot}001$ for all). The only equation to be significantly altered by propranolol administration was that between RR interval and the interval Q to minimum dimension in group A. After propranolol, this became indistinguishable from the corresponding one in group B. The remaining relations were not altered (Table 1). Intervals within the cardiac cycle, such as isovolumic relaxation time or A2 to 'O' point, were independent of RR interval.

INTERACTION BETWEEN PROPRANOLOL AND BASAL CONTRACTION PATTERN

The initial analysis suggested that propranolol might affect the degree of incoordinate contraction, and therefore that basal contraction pattern might be a factor determining its action in individual patients. For this reason, patients with synergic (group A) and asynergic (group B) contraction in the basal state were considered separately (Table 2).

Control values

In group A (nine patients), the timing of A2 with respect to minimum dimension was normal, by definition. There was thus a slight drop in cavity dimension during isovolumic relaxation. Time relations between dimension and apexcardiogram were normal, both during isovolumic contraction and relaxation, as were peak VCF and peak rate of dimension increase during diastole. In group B (7 patients), defined on the basis of the abnormal timing of A2 with respect to minimum dimension, significant disturbances were also present in apexcardiogram dimension relations. There was a 14 per cent fall in dimension during the time of inscription of the upstroke, and a 34 per cent (range 8 to 71%) during the downstroke (normal, up to 33%). In addition, there was an abnormal dimension increase of 16 per cent (range 0 to 42%) during isovolumic relaxation. The time interval from the Q wave to minimum dimension was 95 ms shorter than in group A ($p < 0{\cdot}001$), and that from Q to 'O' point 45 ms less ($p < 0{\cdot}01$). The interval from minimum dimension to mitral valve opening was greatly prolonged to 90 ms, compared with 15 ms in group A ($p < 0{\cdot}001$), and that from A2 to 'O' point shorter by approximately 40 ms ($p < 0{\cdot}01$). The RR interval was slightly less in group B, but this difference was not statistically significant. In group B patients, therefore, there was evidence both of asynchronous contraction, and abnormalities of relaxation.

Effect of propranolol in group A (Fig. 2 and 3)

Intravenous propranolol administration was associated with a significant increase in RR interval from 910 to 1045 ms ($p < 0{\cdot}05$). There were minor changes in the two intervals Q to mitral valve opening and minimum dimension to A2, each significant at the 5 per cent level. Peak rate of dimension increase during diastole fell ($p < 0{\cdot}01$). The effects of oral propranolol were significantly different. Though the increase in RR interval was less than after intravenous propranolol, there was a very significant drop in Q to minimum dimension by 50 ms ($p < 0{\cdot}01$), so that mitral valve opening was delayed with respect to minimum dimension by 65 ms ($p < 0{\cdot}01$). In spite of the delay, however, left ventricular dimension increased by only 8 per cent during isovolumic relaxation, very significantly less than the corresponding figure in group B patients with asynchronous contraction ($p < 0{\cdot}001$). There was no significant change in left ventricular dimensions or peak VCF after either oral or intravenous propranolol.

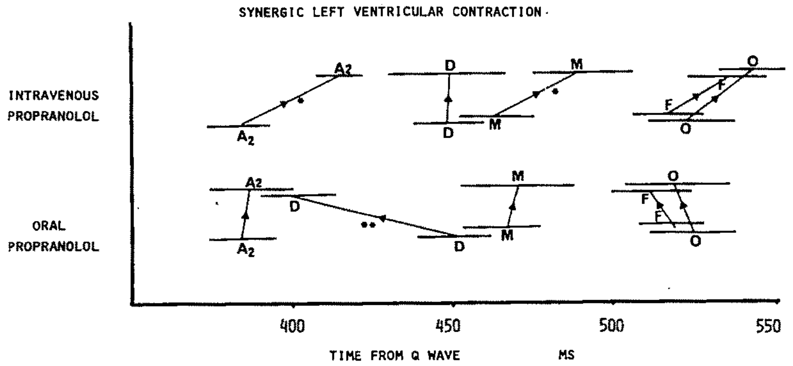

Fig. 3 *Effects of intravenous or oral propranolol on diastolic events in group A patients. The intervals from Q to A2, minimum dimension (D), mitral valve opening (M), the 'O' point (O), and peak filling (F) are shown as bars, whose length represents two standard deviations about mean values. Arrows point from control values to those after administration of the drug. Statistical significance of changes:* *, $p > 0{\cdot}05$; **, $p > 0{\cdot}01$.

Effect of propranolol administration in group B

The effects of propranolol administration to patients with asynchronous contraction were more complex and virtually the same whether the drug was given intravenously or orally (Fig. 4). There was significant slowing of the heart rate ($p < 0.05$). The timing of minimum dimension with respect to the Q wave, already abnormally early in the control state, was unaffected, in contrast to the results after oral propranolol administration to patients in group A. However, the timing of a number of diastolic events was delayed with respect to the Q wave, including mitral valve opening ($p < 0.01$), the 'O' point ($p < 0.01$), and, after oral propranolol only, the discontinuity on the dimension trace at the end of rapid filling ($p < 0.01$). Isovolumic relaxation was prolonged by 20 to 30 ms ($p < 0.001$ intravenous, $p < 0.01$, orally), and the interval A2 to 'O' point by 40 ms ($p < 0.01$ iv, $p < 0.05$ orally). After either oral or intravenous propranolol, there was a further increase in dimension during isovolumic relaxation ($p < 0.05$), and peak rate of dimension increase was reduced ($p < 0.05$). There was no significant change in arterial pressure in either group.

Discussion

M-mode echocardiography has significant advantages for studying the action of drugs in man. Left ventricular cavity size and peak rate of dimension change can be measured with unequivocal localisation of the endocardium at a frequency response of 1000/s. The method can also be used to detect incoordinate wall movement during isovolumic contraction and early relaxation,[10 11] prolongation of isolvolumic relaxation, and abnormalities of dimension change during filling with results that agree closely with cineangiography. Though the distribution of asynergic areas cannot be determined, their physiological effects are shown in a manner well suited for clinical pharmacological studies.

It has previously been shown that propranolol administration causes minor changes in left ventricular dimensions and mean Vcf.[12–14] These effects are small, being of the same order as the reproducibility of the method, and no longer occur when changes in heart rate or arterial pressure are prevented with atropine or phenylephrine.[12] Our results are similar to these. Changes in the intervals Q to A2, minimum dimension, and mitral valve opening in normal subjects were all explicable on the basis of heart rate. The results in patients with coronary artery disease showed wider scatter, but there were significant reductions in peak Vcf and the rate of dimension increase during diastole, and also in the extent of overall dimension shortening during systole.

When the patients were divided into two groups dependent on basal contraction pattern, however, well-defined effects of propranolol became apparent. Though a single criterion, the timing of A2 with respect ot minimum dimension, was used to define asynergic contraction, patients identified in this way differed from the remainder in showing other evidence of incoordinate contraction, including abnormal dimension changes during isovolumic contraction and early relaxation as well as delay in mitral valve opening.

In patients with a synergic contraction pattern in the control state, intravenous propranolol had identical effects to those seen in the normal group. With chronic oral administration, however, the normal reduction in left ventricular dimension during isovolumic relaxation did not take place. Minimum dimension therefore occurred early with respect to the Q wave, the reverse of what would be predicted from the drop in heart rate (Fig. 2). Since the duration of electromechanical systole was unaltered, A2 came to be synchronous with minimum dimension. Isovolumic relaxation time re-

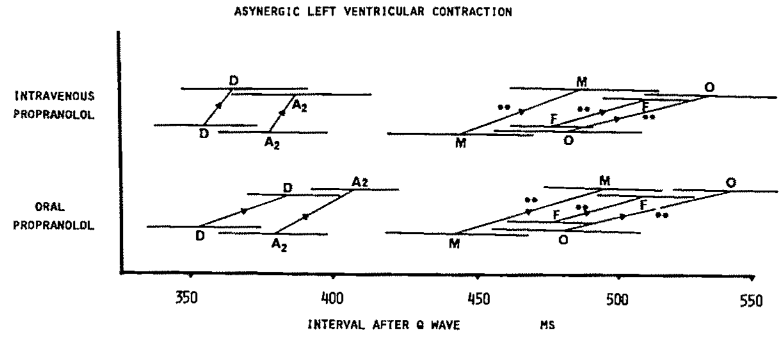

Fig. 4 *Effects of intravenous or oral propranolol on diastolic events in group B patients. Layout as in Fig. 3.*

mained constant, so that mitral valve opening was now delayed with respect to minimum dimension rather than being synchronous with it. In spite of this, dimension increased by only 8 per cent during isovolumic relaxation, in contrast to the 23 per cent seen in patients in the asynergic group during the same period. Neither oral nor intravenous propranolol caused incoordinate contraction to appear or the timing of diastolic events to be altered. The reason for the difference between oral and intravenous propranolol on the timing of minimum dimension was not clear, though it is reminiscent of similar differences in action between acute intravenous and chronic oral propranolol administration on peripheral resistance in hypertensive patients.[15 16]

The effects of propranolol in patients with evidence of asynergic contraction under basal conditions were quite different. Q-A2 interval was normal for heart rate, and remained so. In the control state, Q to minimum dimension was already approximately 80 ms shorter than that predicted from heart rate in normal subjects, and was unaffected by propranolol. Instead, a series of diastolic abnormalities appeared, which included further delay in mitral valve opening, prolongation of isovolumic relaxation, delay in the timing of the 'O' point with respect to A2, and a reduction in the peak rate of dimension increase during diastole, whose timing now came to coincide with the onset of mitral valve opening. At the same time, relaxation became more incoordinate, with a further increase in dimension during the period before mitral valve opening and the 'O' point of the apexcardiogram. It is possible that these contrasting effects of propranolol in our two groups of patients might explain apparent contradictions in previous descriptions of its action on regional left ventricular wall movement in patients with ischaemic heart disease.

Diastolic abnormalities induced by propranolol have received little attention, and their genesis is not entirely clear. Two were seen in the present study. We cannot explain the reduction in the time interval from Q wave to minimum dimension. It was the reverse of that predicted from the fall in heart rate, and could not be ascribed to any change in arterial pressure. Its basis was loss of the normal reduction in dimension during isovolumic relaxation, which itself is brought about by an increase in posterior wall thickness.[17] In our patients, therefore, thinning began prematurely. This occurred under two clearly defined sets of conditions; either as a manifestation of asynergic contraction in the control state or as an effect of propranolol administration to patients with ischaemic heart disease in whom contraction was initially synergic. Pre-existing left ventricular disease was a necessary condition for its appearance, since it was not seen after propranolol administration to normal subjects. It was not simply caused by beta-blockade, because it did not occur after intravenous propranolol in spite of a significant fall in heart rate. It was not the result of a negative inotropic stimulus modifying the relation between end-systolic pressure and volume,[18] because the dominant abnormality was one of dimension and wall thickness change during isovolumic relaxation rather than ejection. Finally, the two mechanisms causing shortening of the interval Q-minimum dimension were not additive, since propranolol had no further effect in patients with asynergic contraction in whom it was already short in the control state. This suggests that maximum possible shortening has occurred when A2 is synchronous with minimum dimension. The mechanism underlying the normal dimension reduction during isovolumic relaxation, in being sensitive to this effect of left ventricular disease or propranolol, can thus be distinguished from that operating during ejection, which is not.

The second diastolic abnormality induced by propranolol was to increase the delay in mitral valve opening and to aggravate abnormalities of wall movement during filling in patients with asynergic contraction. This is unlikely to have been a direct effect of the drug on relaxation, since it did not appear in normal subjects or in patients with synergic contraction. It has previously been shown that in patients with coronary artery disease, delayed mitral valve opening and incoordinate wall movement during filling are frequently caused by asynchronous termination of systole in different regions of the cavity, rather than being a primary disturbance of relaxation.[19] This causes A2 to be delayed with respect to minimum dimension,[8] the criterion we used to define patients with asynchronous contraction. Propranolol could thus aggravate diastolic abnormalities simply by exacerbating differences in timing between normal and abnormal regions of the ventricle. Its lack of effect on wall movement during isovolumic contraction in all our patients as well as its failure to induce relaxation abnormalities in those in whom contraction is initially synergic suggest that propranolol aggravates incoordination by increasing the effects of abnormalities already present rather than by inducing new ones.

The effects of propranolol on left ventricular wall movement in patients with coronary artery disease are thus complex. There was no demonstrable increase in end-diastolic dimension, probably because the patients were studied supine, with the pericardium preventing any significant increase in cavity size. There was a uniform reduction in heart rate and a slight fall in peak VCF, both compatible with blockade of sympathetic activity present under control conditions in these patients, many of whom had severe left ventricular disease. The main effects, however, were to be seen during the early phases of relaxation, and were determined by the state of left ventricular function in the control state. It follows that the effect of propranolol in patients in whom it is to be used therapeutically cannot be predicted from the results of studies in normal subjects. It also rppears that incoordinate left ventricular contraction of the type seen in ischaemic heart disease can be modified pharmacologically. Finally, and in more general terms, the investigation of drug action by echocardiography can be extended from simple measurements of small dimensional changes to the determination of the timing and relation of wall movement to a series of well-defined events throughout the cardiac cycle, identified with additional information from the phono- and apexcardiogram. Such methods may be regarded as an extension of those previously established using the systolic time intervals, and, as with the latter, it is possible to make appropriate allowance for the effects of changes in heart rate. A significant improvement in specificity is obtained, however, when information from the digitised M-mode echocardiogram is included, so that it becomes possible to study diastolic as well as systolic events, and to undertake a complex analysis of left ventricular wall movement in a manner not easily accessible even to standard invasive techniques.

The authors thank Dr S Oram for co-operation, and Deutsche Forschungsgemeinschaft for support.

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Br Heart J 1980; **43:** 301–305

Coagulation studies in rheumatic heart disease

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SUMMARY The clotting characteristics of pulmonary and systemic blood were studied in 10 patients with chronic rheumatic mitral valve disease complicated by atrial fibrillation and in seven patients with aortic valve disease in sinus rhythm. A haemostatic basis for the association of rheumatic mitral valve disease with thrombotic emboli was sought.

Both groups of patients showed differences in platelet function between pulmonary and systemic arterial blood. In patients with mitral valve disease aggregation of platelets was significantly greater in pulmonary than in systemic arterial blood at rest; the converse was true during exercise. In aortic valve disease platelet aggregation was greater in systemic than in pulmonary arterial blood at all times. Only the patients with mitral valve disease showed changes in blood coagulation during passage through the lungs and left heart; there was a small but statistically significant shortening in partial thromboplastin time in systemic as compared with pulmonary arterial blood both at rest and during exercise. Similarly, the effects of exercise on the various haemostatic factors measured were largely confined to the patients with mitral valve disease; in these patients exercise stimulated an increase in factor VIII in pulmonary arterial blood and an increase in platelet adhesiveness and aggregability in left heart blood. These changes provide a basis for the suggestion that in patients with rheumatic mitral valve disease, unlike those with aortic valve disease, there is an increased thrombotic tendency in blood in the left heart which is particularly pronounced during exercise.

Systemic emboli are a serious hazard of rheumatic mitral valve disease.[1 2] The risk does not appear to be related to the type of valvular deformity,[3] or haemodynamic derangement.[4] Though relevant, few studies have been reported of possible abnormalities in the clotting characteristics of blood as it passes across the damaged mitral valve. The following study was undertaken to determine whether such abnormalities exist.

Subjects and methods

Seventeen patients were studied. Ten, including six women, had moderate or severe mixed mitral valve disease complicated in all by chronic atrial fibrillation. Seven patients, including four women, with mild aortic valve disease in sinus rhythm furnished a control population. Clinical diagnosis in all was confirmed by angiographic and haemodynamic studies. No patient was in congestive heart failure, none had a history of embolic episodes, and none had taken anticoagulants. All gave their consent for the study which was agreed by the hospital ethical committee.

DESIGN OF STUDY

(a) *In vitro studies*

These were undertaken to determine the effect of the passage of blood through the catheters used in the in vivo study. Peripheral venous blood was taken from eight healthy volunteers (four men, four women) into plastic syringes without anticoagulation. Blood was taken into three syringes; from the first syringe blood was transferred direct to 1/9 volume 3·8 per cent sodium citrate, and from the second and third syringes was passed, respectively, through the pulmonary (8F US Catheter Co. Ltd.) or the arterial (75 × 0·2 cm Portex Ltd.) catheter. The first 5 ml blood passing through each catheter were discarded and the remainder collected in the appropriate tubes for platelet and coagulation factor measurements.

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Received for publication 17 July 1979

(b) *Comparison of blood clotting variables in pulmonary and systemic arterial circulations*

Measurements were made at the time of routine diagnostic haemodynamic evaluation. Blood samples were withdrawn simultaneously from the pulmonary and systemic arteries at rest and at the end of two minutes of submaximum supine bicycle exercise. Pulmonary arterial blood was withdrawn through a woven Dacron catheter (8F US Catheter Co. Ltd.) and aortic blood through a nylon catheter (75 × 0·2 cm Portex Ltd.). No anticoagulants were used; catheters were kept patent by saline infusion.

The first 10 ml blood withdrawn from each catheter were discarded. Samples were then taken into plastic syringes and mixed with heparin (40 IU/10 ml), for platelet adhesion studies, with 1 per cent tranexamic acid for fibrin related antigen measurement, with EDTA for platelet counts, and with 1/9 volume 3·8 per cent sodium citrate for the remaining tests.

The citrated blood was spun at 250 *g* for 15 minutes to obtain platelet rich plasma which was drawn off with a siliconised pipette. The remainder of the blood was spun at 2500 *g* for 20 minutes at 4°C to obtain platelet poor plasma.

Platelet counts were performed on a Coulter thrombocounter. Coagulation studies were performed by the following methods:

Activated partial thromboplastin time[5]; fibrinogen[6]; plasminogen[7, 7a]; urokinase sensitivity[8]; euglobulin lysis time[9]; fibrinogen related antigen[10]; factor VIII[11]; platelet adhesiveness[12]; platelet aggregation[13]; platelet factor 3.[14]

Platelet aggregation was measured in response to adrenaline (acid bitartrate, Sigma Chemical Co., St. Louis), to ADP (Sigma Chemical Co., St. Louis), and to soluble collagen.[15] These agents were diluted in tris-buffered saline pH 7·4 and added to the platelet rich plasma in amounts to give final concentrations of 5 µmol adrenaline and 0·5, 2·0, and 4·0 µmol ADP. A quantitative assessment of platelet aggregation was made by measuring the slope of the changes in light transmission (IR), the amount of light transmission three minutes after addition of the aggregation agent (T_3), and the maximal light transmission achieved (T max) within three minutes.

Results

CATHETER EFFECTS ON BLOOD CLOTTING VARIABLES

The results are summarised in Table 1. No statistically significant difference was noted in any of the indices studied between the blood that was and was not passed through arterial or pulmonary catheters.

Table 1 *Comparison of effects of passage of non-anticoagulated peripheral venous blood from healthy volunteers through pulmonary and arterial catheters (mean values ± standard error of mean)*

Variables		*Before catheter transit*	*Pulmonary catheter*	*Arterial catheter*
Partial thromboplastin time (s)		30·3 ±1·1	31·9 ±1·8	30·4 ±1·2
Platelet count ($\times 10^9$)		241 ±17·7	247 ±18·7	236 ±14·9
Platelet aggregation to				
0·5 µmol ADP	IR	25·1 ±3·6	27·7 ±4·8	26·8 ±4·1
	T_3	3·1 ±1·7	3·3 ±1·3	2·7 ±1·3
	T max	7·6 ±1·5	8·0 ±1·8	7·8 ±1·6
2·0 µmol ADP	IR	73·3 ±3·9	74·8 ±6·7	72·3 ±4·7
	T_3	52·6 ±6·0	49·1 ±6·4	51·1 ±5·1
	T max	55·0 ±3·7	47·8 ±6·7	52·3 ±4·1
collagen	IR	105·8 ±5·5	100·7 ±4·6	96·2 ±4·6
	T_3	63·9 ±1·2	63·4 ±0·9	61·1 ±2·0
4 µmol adrenaline	IR	26·6 ±4·5	31·6 ±4·9	27·3 ±4·9
	T_3	51·4 ±3·7	49·0 ±5·1	49·7 ±4·6
Factor VIII		132 ±8·7	125 ±10·9	128 ±10·9
Platelet adhesion (%)		46·4 ±7·5	48·0 ±8·3	44·4 ±7·5
Plasminogin (casein units/ml)		3·1 ±0·2	3·3 ±0·2	3·1 ±0·2
Fibrinogen (g/l)		1·9 ±0·2	2·0 ±0·1	1·9 ±0·1
Euglobulinysis time (min)		332 ±50·0	329 ±47·8	319 ±48·9

No statistically significant difference was noted between the three sets of determination.

COMPARISON OF HAEMOSTATIC FACTORS IN PULMONARY AND SYSTEMIC ARTERIAL BLOOD

Factors in which there was a statistically significant difference are detailed in Table 2.

In mitral valve disease

At rest: there was a small decrease in activated partial thromboplastin time and a decrease in platelet aggregation in aortic as compared with pulmonary arterial blood.

During exercise: the small atrioventricular difference in PTT was maintained accompanied by a significant decrease in platelets and an increase in platelet aggregation (to 2·0 µmol ADP T max) in aortic as compared with pulmonary arterial blood.

In aortic valve disease

At rest: there was a significant increase in platelet aggregation in aortic as compared with pulmonary arterial blood.

During exercise: the increase in platelet aggregation in aortic blood was maintained.

CHANGES IN HAEMOSTATIC FACTORS INDUCED BY EXERCISE

Factors in which there was a statistically significant

Table 2 *Statistically significant changes in haemostatic measurements: effects of transit through pulmonary circulation and left heart—mean values are presented*

Variable		*Mitral valve disease*				*Aortic valve disease*			
		Rest		*Exercise*		*Rest*		*Exercise*	
		Pulmonary	*Systemic*	*Pulmonary*	*Systemic*	*Pulmonary*	*Systemic*	*Pulmonary*	*Systemic*
PTT (s)		36 ±2	34 ±1*	35 ±2	33 ±1‡	—	—	—	—
Platelet count ($\times 10^9$)		—	—	231 ±37	202 ±28*	—	—	—	—
Platelet aggregation to									
0·5 µmol ADP	IR	48 ±11	35 ±10‡	—	—	42 ±8	56 ±8*	—	—
	T_3	5·4 ±1·4	3·1 ±1·1†	—	—	—	—	11·8 ±2·7	14·7 ±2·8‡
2·0 µmol ADP	T max	—	—	33 ±5	44 ±6*	—	—	—	—
	T_3	—	—	—	—	42 ±9	55 ±7*	—	—
Collagen	IR	81 ±8	63 ±9*	—	—	—	—	—	—
	T_3	67 ±3	55 ±6*	—	—	—	—	—	—
Adrenaline	T_3	—	—	—	—	30 ±4	39 ±6*	—	—

* $p<0·05$; † $<0·02$; ‡ $<0·01$.

difference are detailed in Table 3.

In mitral valve disease
Exercise was associated with an increase in factor VIII in pulmonary arterial blood and an increase in platelet adhesion and aggregation in systemic arterial blood.

In aortic valve disease
Exercise was associated with an increase in platelet aggregation in pulmonary arterial blood; there were no changes in any of the other haemostatic factors measured in either pulmonary or aortic blood.

Discussion

These observations demonstrate a number of differences between the clotting factors in the pulmonary and systemic arterial blood of patients with advanced mitral valve disease and those in a control population of patients with mild aortic valve disease. As shown in Table 1, passage through the different catheters produced only trivial and statistically insignificant changes in the haemostatic function tests.

The most pronounced changes found in the patient studied were seen in platelet function. At rest platelet aggregation was less in systemic than in pulmonary arterial blood in patients with mitral valve disease; in patients with aortic valve disease the converse was true. During exercise both groups showed an increase in platelet aggregation in systemic as compared with pulmonary arterial blood, and in the patients with mitral valve disease this was accompanied by a diminution in aortic platelet count. Exercise was responsible for a pronounced increase in platelet adhesion and aggregation in aortic blood in mitral valve disease; in contrast, changes in aortic valve disease were confined to a limited increase in aggregation in pulmonary blood.

Before attempting to interpret these complex changes it is well to examine the limitations imposed by the design of the study. None of the patients with mitral valve disease had had emboli; the haemostatic factors in this cohort may, therefore, be quite different from those in a group of patients who had suffered such an event. The control group of patients with aortic valve disease was chosen for ethical reasons. However, their valve lesion was

Table 3 *Statistically significant changes in haemostatic measurements: effects of exercise—mean values are presented*

Variable		*Mitral valve disease*				*Aortic valve disease*			
		Pulmonary arterial		*Systemic arterial*		*Pulmonary arterial*		*Systemic arterial*	
		Rest	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*	*Rest*	*Exercise*
Factor VIII		107 ±5	120 ±7*	—	—	—	—	—	—
Platelet adhesion (%)		—	—	59 ±7	63 ±6†	—	—	—	—
Platelet aggregation to									
0·5 µmol ADP	IR	—	—	35 ±10	57 ±12‡	42 ±8	65 ±12*	—	—
	T_3	—	—	3·1 ±1·1	8·0 ±2·3‡	—	—	—	—
	T max	—	—	12·8 ±3·4	21·5 ±4·2‡	—	—	—	—
Collagen	IR	—	—	63 ±9	95 ±8‡	—	—	—	—
	T_3	—	—	55 ±6	68 ±2†	—	—	—	—

*$p<0·5$; †$p<0·02$; ‡$p<0·01$.

mild, all were in sinus rhythm, and their clinical state was such as to warrant their inclusion as reasonable control population. It could also be argued that a higher workload or longer periods of exercise would have induced more pronounced changes. This may indeed be true, but both were at the limits ethically justifiable during investigation of patients with mitral valve disease. Finally, it must be emphasised that the pulmonary systemic arterial differences in blood clotting factors measured describe only composite changes; they allow no separation of the particular effects of transit through the lesser circulation from those occurring during passage through the left atrium and over the damaged mitral valve.

Despite these design limitations, the results are interesting. The reduction in platelet aggregation after passage through the pulmonary circulation and left heart at rest in patients with mitral valve disease contrasts with the reverse situation in aortic valve disease. However, during exercise which can be expected to increase platelet stickiness,[16] there was an increase in platelet aggregation in systemic as compared with pulmonary arterial blood in both groups; in the patients with mitral valve disease there was additionally a coincidental reduction in the systemic arterial platelet count. The interpretation of these changes in pathological terms is speculative. It can be reasoned that in the patients with mitral valve disease at rest, many of whom have shortened platelet survival,[17] the more sticky platelets were sequestered in the pulmonary blood vessels or left heart during the retarded passage of blood through the lesser circulation. There is a substantial incidence of pulmonary arterial intimal damage and atheroma in patients with pulmonary hypertension caused by mitral valve disease; such intimal lesions could be expected to form a nidus for deposition of the most sticky platelets. There is no large platelet pool in the lesser circulation,[18] so that the more rapid flow of blood through the lungs during exercise could be expected to reverse this trend, as was observed. However, these speculations are at variance with the observations of Kallinkos-Maniatis,[19] who found a significantly *greater* platelet count in systemic as compared with central venous blood in patients with a range of cardiac diagnoses. The difference in our findings could possibly be explained by differences in the techniques of measurement used and the patients in the two studies.

Recently published observations[20 21] have shown that in a number of animal species the lungs are the site of continuous generation of prostacyclin (PGI_2) the most potent inhibitor of platelet aggregation so far described, and that vigorous hyperventilation increases release from the lungs of a platelet disaggregating agent. Piper and Vane[22] showed that injection of particles into guinea-pig lungs led to release of prostaglandins, except when the injections led to an increase in pulmonary arterial pressure when there was no detectable release of prostaglandins. It may be that our studies in man can be explained on the basis that the aortic valve disease 'control' patients mimic the general animal response cited above and that mitral valve disease patients with their damaged lungs and pulmonary arterial hypertension at rest mimic the guinea-pigs and only behave as the aortic valve disease patients do after the stimulus of exercise and the associated increase in ventilation.

The only other difference in haemostatic changes between the two groups was in the blood coagulation screening test, PTT. Activated PTT was less in systemic than in pulmonary arterial blood both at rest and during exercise in patients with aortic valve disease. In the group with mitral valve disease exercise also increased factor VIII activity, confirming other reports.[23] Again, though the pathological interpretation of these findings is speculative, the increase in factor VIII activity during exercise and the reduction in PTT during passage of blood through the lesser circulation could possibly be expected to increase the tendency to thrombus formation, particularly in atheromatous pulmonary vessels or left atrium, the seat of endocardial damage or excessive blood stasis.

These studies give no clue as to the mechanisms involved in these platelet and blood coagulability changes in patients with mitral valve disease, but they prompt an interesting speculation. The prime characteristic of impaired cardiac function is reflex activation of the sympathoadrenal system and a raised concentration of catecholamines in the plasma.[24] These changes are particularly noticeable in patients with mitral valve disease and increase during exertion. Such sympathoadrenal activation can be expected to stimulate the breakdown of energy-rich ATP to ADP in the tissues and blood cells and thus enhance the adhesiveness of platelets and their tendency to aggregation.

Whatever the mechanisms involved, our findings are consistent with the fact that patients with mitral valve disease do indeed have an increased tendency to platelet deposition and thrombin formation followed by fibrin deposition in the lesser circulation and left heart. This is not to imply that such changes are the primary cause of clotting events in these patients. It is much more likely that the tardy blood flow, the high pressures in the pulmonary vessels and left atrium, and the intimal damage in these vascular compartments are the basic pathogenic factors. However, our results are fully compatible with the haemostatic changes that could be expected in such a situation. They also give theoretical support to the practical therapeutic observations that in mitral valve disease anticoagulants reduce the incidence of arterial embolism,[1 25] and that antiplatelet agents do so in patients after mitral valve surgery.[26] Clearly, more work is necessary, and results give impetus for such endeavours.

We are grateful to the Special Trustees of the General Infirmary for financial support.

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Br Heart J 1980; **43**: 306–314

Effect of prostaglandin E_1 on pulmonary circulation in pulmonary atresia

A quantitative morphometric study

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SUMMARY The structural effect of prostaglandin E_1 on the pulmonary circulation in pulmonary atresia has been studied by applying quantitative morphometric techniques to the injected and inflated lungs of eight babies who had received prostaglandin E_1 for between 30 hours and 12 days.

The most striking effect was on the pulmonary arterial smooth muscle. Relative arterial medial thickness was reduced and muscle did not extend as far along the arterial pathway as compared with the normal and with untreated cases of pulmonary atresia, dying at a similar age. The reduction in muscularity tended to increase the longer the duration of infusion. In all cases the thin arterial media was less compact than normal, and localised aneurysmal dilatations occurred, varying in extent and severity between cases. The preacinar arteries were dilated in comparison with the untreated cases, but, by contrast, the intra-acinar arteries remained abnormally small. The number of intra-acinar arteries per unit area of lung was greater in prostaglandin E_1 treated than in untreated cases.

Infusion of prostaglandin E_1 is now the ideal emergency treatment for pulmonary atresia, but the findings in the present study suggest that it should be given for as short a time as possible before the pulmonary blood flow is increased by surgical treatment.

Prostaglandin E_1 (PGE_1) dilates the ductus arteriosus[1] and is therefore used in the emergency treatment of newborn infants with pulmonary atresia.[2] The effect of PGE_1 on the lungs of such patients is unknown. Acute experiments on healthy fetal and newborn goats,[3 4] and in the adult animal in a variety of species,[5–7] demonstrate a fall in pulmonary vascular resistance. In the human adult infusion on PGE_1 lowers pulmonary vascular resistance, considerably in the presence of pulmonary hypertension, but only slightly in the normal lung.[8 9]

A quantitative morphometric study of the lungs of untreated children dying with pulmonary atresia showed a reduction in pulmonary arterial muscle, pre- and intra-acinar arterial size, and intra-acinar arterial number,[10] compared with normal.[11 12] In the present study the effect of PGE_1 on the lung vessels of patients with pulmonary atresia, dying at a similar age, has been analysed using the same techniques.

Received for publication 17 August 1979

Subjects

The lungs of eight patients with pulmonary atresia were examined (Table 1). All children underwent surgical treatment. In four children an aortopulmonary anastomosis was performed, in three a Brock procedure, one of whom also had formalin infiltration of the ductus arteriosus, and, in the remaining case, the right ventricular outflow tract was reconstructed. PGE_1 was given preoperatively in all cases and continued after operation in cases 3 and 8. The dose of PGE_1 given varied between 0·01 and 0·1 μg/kg per min, the majority of patients receiving at least 0·08 μg/kg per min for most of the time.

Preoperative infusion of PGE_1 produced a clinical improvement in all cases. The increase in systemic arterial oxygen tension varied between 8 and 20 mmHg (mean 13 mmHg). Five children survived surgery, but only case 5 appeared to have had a significant increase in pulmonary blood flow. He

Table 1 *Clinical data*

Case no.	*Age PGE$_1$ started (h)*	*Duration (h)*	*Dose (µg/kg per min)*	*Route*	*Time interval between end of PGE$_1$ infusion and death (d)*	*Age at death (d)*
1	14	30	0·04–0·08	Aorta	0	2
2	10	72	0·05–0·10	Peripheral vein	0	4
3	24	74	0·01–0·12	Umbilical vein	0	5
4	12	6 d	0·02–0·10	Umbilical and peripheral vein	4	23
5	24	12 d	0·01–0·05	Aorta	3	16
6	41	15	0·02–0·10	Umbilical and peripheral vein	13	15
7	8 d	8	0·1	Aorta	8 h	9
8	40 d	29	0·01–0·10	Peripheral vein	7	50

died three days after operation with disseminated intravascular coagulation.

The structural findings are compared with those in a published series, consisting of six 'untreated' cases of pulmonary atresia who did not receive PGE$_1$ and died without effective surgical treatment at between 1 and 28 days of age.[10]

Methods

The pulmonary arteries to both lungs were injected in all, save case 7, where the right pulmonary artery and left pulmonary veins were injected. A Micropaque gelatin suspension at 60°C was injected at a pressure of 100 cm of water: this injection technique distends and fills all vessels larger than 15 µm in diameter. The lungs were then inflated with a buffered formol saline solution at a pressure of 45 cm of water and allowed to fix. Lung volume was determined by water displacement, and each lung radiographed and sliced,[13 14] blocks of tissue being selected for microscopical examination by a random sampling technique.[15]

QUANTITATIVE ANALYSIS OF STRUCTURAL FEATURES OF LUNG

From the arteriogram the following features were assessed: hilar and intrapulmonary pattern of branching and the density of the background haze which reflects the number of small peripheral arteries[16]; lumen diameter of the posterior basal arterial pathway measured at the hilum and at 25 per cent intervals from the hilum to the pleural surface.

Microscopically, the following features of peripheral arterial structure were studied: (1) The external diameter and medial thickness of an individual artery was measured and the mean percentage medial thickness calculated. (2) The structure of the arterial wall, whether muscular, partially muscular, or non-muscular was related to size in the large population of vessels. (3) Where a small artery accompanies a small airway it is characterised by reference to the type of airway it accompanies. Thus the structure of an artery could be related to airway level and in this way extension of muscle along the arterial pathway was established. (4) The number of arteries and alveoli were counted in the same area of lung section and the result expressed as a ratio: this made allowance for any difference in the degree of inflation in various lungs. (5) The proportion of lung volume occupied by various structures was established by a microscopical point-counting technique.[15]

Results

In all cases lung volume was within normal limits. Arteriography showed a normal arterial branching pattern in all cases (Fig. 1). Aneurysmal dilatation of the distal half, the muscular portion of the arterial pathway, occurred in all cases, but was pronounced in four (cases 4, 5, 6, and 7) (Fig. 1). In these four cases, between three and seven segments were involved in each lung.

GENERAL HISTOLOGICAL FEATURES

In all cases the arteries accompanying small bronchi and bronchioli were larger than normal relative to the size of the airway and appeared tortuous. Tortuosity extended from at least the level of the small bronchi down the arterial pathway to respiratory bronchiolar level, involving muscular, partially muscular, and non-muscular vessels. Dissecting aneurysms were seen in four cases, involving the preacinar* muscular arteries. The arteries also appeared abnormally thin walled. The elastic fibres and muscle cells were arranged in a less compact fashion than normal, particularly the outermost elastic lamina which frequently peeled away from the vessel at some point around the circumference. Oedema produced small clear spaces, which were variable in size and frequently separated the medial components. These spaces showed no eosinophilia.

Dilatation of the lymphatic channels was a striking feature in cases 1 to 4. In these four cases the subpleural lymphatic channels, those in the connective tissue septa within the lung and those in the perivascular sheath were abnormally distended. Lymphatic dilatation was present but less distinct in cases 5 and 6. In all cases the veins also appeared unduly prominent, appearing larger and more circular than is normal. Vein wall structure appeared normal.

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*An acinus is all the lung tissue distal to a terminal bronchiolus.

ARTERIAL SIZE

On the postmortem arteriogram the lumen diameter of the preacinar arteries was generally greater than that of untreated patients dying with pulmonary atresia and similar to that seen in the normal child of similar age (Fig. 2). The difference in size between untreated and PGE_1 treated cases of pulmonary atresia was pronounced along the proximal half of the pathway, which consists of elastic arteries. Further along the pathway, however, microscopical examination revealed conspicuous dilatation of the preacinar muscular vessels.

By contrast, within the acinus microscopical measurement showed a reduction in external diameter in seven cases (Table 2). At nearly all levels along the arterial pathway the arteries were smaller, even at 15 days, than is seen in the normal lung at three days, and were similar in size to those of untreated patients. In the remaining case (case 8) the findings were difficult to interpret because there were no normal or untreated cases of pulmonary atresia of similar age with which to make a comparison.

NUMBER OF INTRA-ACINAR ARTERIES

In all cases treated with PGE_1, the arterial volume proportion was greater than in untreated cases, and was even greater than normal. The arterial volume proportion varied between 6·9 and 9·4 per cent in PGE_1 treated cases as compared with 1·5 to 3·9 per

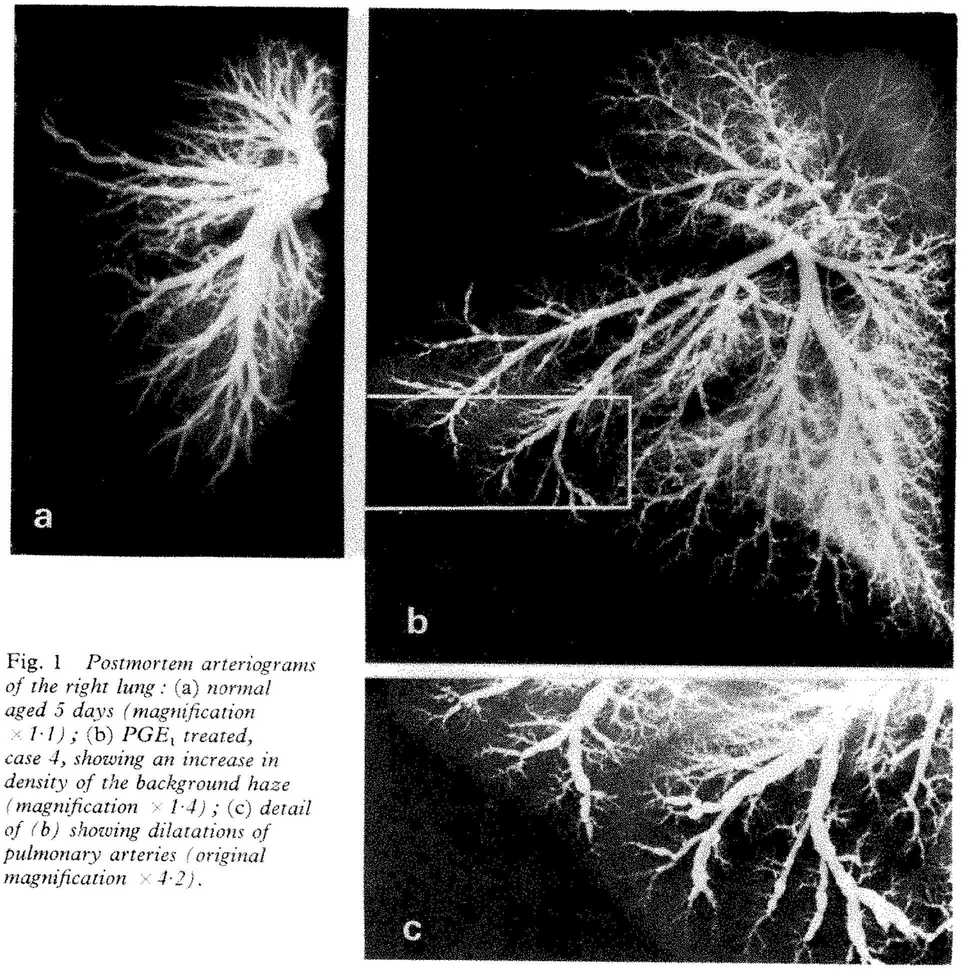

Fig. 1 *Postmortem arteriograms of the right lung:* (a) *normal aged 5 days (magnification × 1·1);* (b) *PGE_1 treated, case 4, showing an increase in density of the background haze (magnification × 1·4);* (c) *detail of (b) showing dilatations of pulmonary arteries (original magnification × 4·2).*

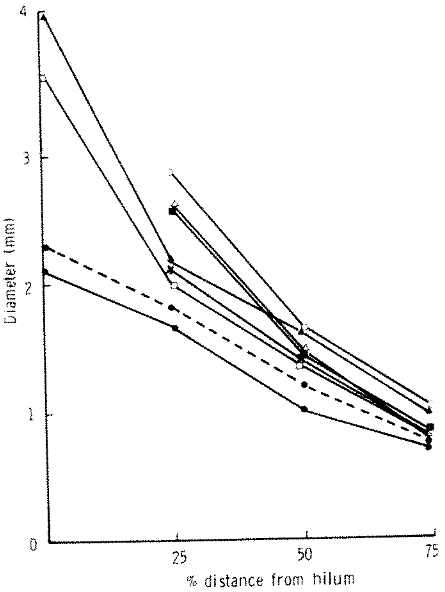

Fig. 2 *Measurements from postmortem arteriograms: lumen diameter (mm) at 25 per cent intervals along the axial pathway from the hilum to the pleural surface is generally greater in PGE*$_1$ *treated than in untreated cases of pulmonary atresia. Interrupted line—mean of five untreated cases of pulmonary atresia (one to 15 days); solid lines—PGE*$_1$ *treated cases of pulmonary atresia (two to 23 days).*

cent in the untreated, and 3·75 per cent in the normal cases. An increase in microscopical arterial volume indicates an increase in the size or number of intra-acinar arteries, or both, but in the present instance suggested an increase in arterial number. In all these cases the postmortem arteriogram showed an increase in density of the background haze, in comparison both with the normal and with the untreated cases of pulmonary atresia (Fig. 1). This observation also suggests an increase in arterial number, confirmed microscopically by finding a reduction in the alveolar/arterial ratio. The ratio varied between 8·6 and 10·69, lower than that of the normal of similar age, 18·9 to 20·3. In untreated pulmonary atresia, peripheral arterial number is reduced, giving an abnormally high alveolar/arterial ratio.

ARTERIAL MUSCULARITY

Percentage arterial medial thickness

In the normal newborn, both human and animal, the postnatal reduction in relative medial wall thickness in arteries smaller than 250 μm in diameter occurs more rapidly than in larger vessels.[12 17] In the present study, therefore, the relative wall thickness in arteries below and above 250 μm diameter was considered separately. In all eight cases relative medial thickness of arteries less than 250 μm was below normal and even below that seen in untreated cases of pulmonary atresia (Fig. 3). In arteries larger than 250 μm, in four cases (cases 1, 2, 3, and 8) muscularity was similar to that seen in untreated cases and below the normal for age. In the remaining four cases muscularity was less than that seen in untreated cases and even less than that seen in the normal adult (Fig. 4). Two of the three cases showing the greatest reduction in muscularity in arteries of all size groups also showed the most severe and widespread picture of aneurysmal dilatations on the postmortem arteriogram.

Extension of muscle along the arterial pathway

Examination of the structure of arteries in relation both to their size and to their position along the arterial pathway showed that in seven cases of pulmonary atresia given PGE$_1$ muscle did not extend as far to the periphery as in either untreated cases of pulmonary atresia or in normal children of similar age. The smaller arteries contained less muscle. The size of the smallest arteries entirely surrounded by a muscle coat was increased and larger arteries had a partially rather than an entirely muscular coat (Table 3). Examination of the structure of arteries accompanying the peripheral airways showed that at terminal bronchiolar level a greater proportion of arteries had a partially muscular rather than an entirely muscular wall (Table 4). More peripherally, at respiratory bronchiolar and alveolar duct level, more arteries had a muscular rather than a partially muscular wall structure. In case 8, the oldest child dying at

Table 2 *Size of arteries accompanying peripheral airways*

		External diameter (μm)			
Case no.	*Age at death (d)*	*Alveolar wall*	*Alveolar duct*	*Respiratory bronchiolus*	*Terminal bronchiolus*
1	2	27·2	42·3	63·8	107·1
2	4	22·8	34·5	76·1	112·0
3	5	22·4	35·4	57·0	98·0
4	23	22·4	42·7	77·8	109·2
5	16	25·2	52·9	85·8	117·0
6	15	28·0	45·8	75·6	149·3
7	9	27·1	44·0	70·5	100·8
8	50	32·8	51·7	123·7	147·2
Untreated pulmonary atresia (n = 5)	1 to 15		32·5 to 61·0	68·2 to 95·0	104 to 143
Normal[12]	3 d to 4 mth	32·1 to 33·0	65·0 to 86·5	92·7 to 122·3	118 to 197

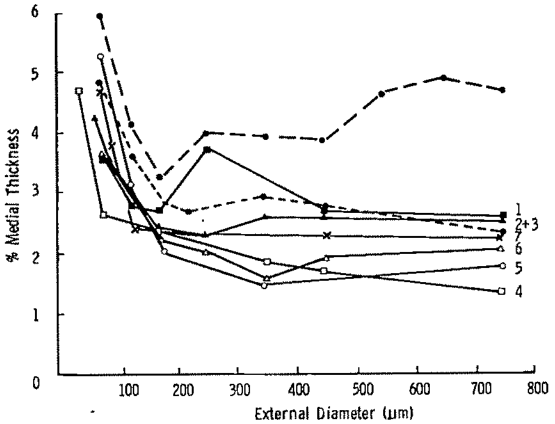

Fig. 3 *Percentage arterial medial thickness related to external diameter (μm), showing the reduction in muscularity in cases of pulmonary atresia given* PGE_1, *as compared with untreated and normal cases.* ●— —● *normal three days;* ●- - - -● *Mean of five untreated cases of pulmonary atresia. Solid lines represent* PGE_1 *treated, numbered cases, of similar age.*

50 days, the distribution of muscle along the arterial pathway was normal.

SUMMARY OF PATHOLOGICAL FINDINGS

Comparison of the PGE_1 treated with the untreated cases of pulmonary atresia and with the normal showed the following: the preacinar arteries were dilated and tortuous, but the intra-acinar arteries remained abnormally small, similar in size to those of untreated cases. The number of intra-acinar arteries per unit area of lung was increased in relation to untreated cases and even exceeded the number found in the normal newborn lung. The lymphatic channels were abnormally distended in four cases. The walls of the muscular and partially muscular arteries appeared oedematous, the media was less compact than normal, and the outer elastic lamina was frequently broken. In the large muscular arteries localised aneurysmal dilatations occurred and dissecting aneurysms were present microscopically in four cases. Pulmonary arterial smooth muscle was reduced. Percentage arterial medial thickness was reduced, and muscle did not extend as far along the arterial pathway as in either the normal or untreated cases of pulmonary atresia.

Discussion

In this series of newborn children with pulmonary atresia treated with PGE_1, the most striking abnormality was a reduction in pulmonary arterial smooth muscle. This feature cannot be attributed to the increase in blood flow achieved by dilating the ductus arteriosus. In congenital heart disease an abnormally high flow is associated with increased pulmonary arterial muscle, even when there is little increase in pressure,[20] and in pulmonary atresia or stenosis an aortopulmonary anastomosis is frequently associated with increased muscularity.[10 21]

The morphological findings in the present study are consistent with the physiological and in vitro studies on the action of PGE_1 on the pulmonary vasculature. PGE_1 relaxes isolated strips of pulmonary vascular smooth muscle, taken from both the mature and fetal animal.[22 23] In acute human, dog, swine, and sheep studies, infusion of PGE_1 reduces pulmonary vascular resistance, though the magnitude of the response is species dependent.[6 7] Holding the pulmonary blood flow constant, PGE_1 lowered the resistance by 51·1 per cent in the fetal goat, a response attributed to pulmonary vasodilatation.[3] The findings of an increased number of injection filled intra-acinar arteries in the present study suggests that recruitment of peripheral arteries may be at least as important as dilatation in helping to reduce pulmonary vascular resistance.[24]

This is the first study to show that prolonged infusion of PGE_1 can, at least in the newborn human lung, produce a reduction in pulmonary arterial smooth muscle. This finding suggests that the effect of PGE_1 on the smooth muscle cells in acute studies is manifested as a structural change after prolonged infusion.

The effects of PGE_1 on the structural properties of the smooth muscle cell are not understood, but PGE_1 is known to change the differentiating state of human skin and lung fibroblasts.[25] These cells respond to PGE_1 by a reduction in collagen synthesis. The response is rapid, a 47 per cent reduction in collagen synthesis appearing after only six hours of exposure to PGE_1. As with systemic and pulmonary arterial vascular smooth muscle cells, fibroblasts exposed to PGE_1 show an increase in cyclic nucleotides.[23 26 27]

In the present study the smooth muscle cells probably became less specialised. Meyrick and Reid[28] showed that the partially muscular and nonmuscular regions of the arterial pathway contain intermediate cells and pericytes. These cells contain fewer contractile filaments than a smooth muscle cell and lie internal to a single elastic lamina. When rats are exposed to hypoxia these cells differentiate to form new muscle.[28 29] Recovery is associated with a reduction in muscularity, and arteries entirely surrounded by muscle become partially muscular and the partially muscular become nonmuscular vessels[30]: these findings are similar to those in children with pulmonary atresia given PGE_1.

Prostaglandin E_1 was given to five children during the first 24 hours of life. Human and animal studies on the normal lung show that it is during the first 24 hours of life that lung structure is changing rapidly and adapting to extrauterine life.[12 17] All the children given PGE_1 showed a greater reduction in muscularity in arteries less than 250 μm in diameter than in either normal or untreated cases. This suggests that PGE_1, given at a time when the pulmonary circulation is probably

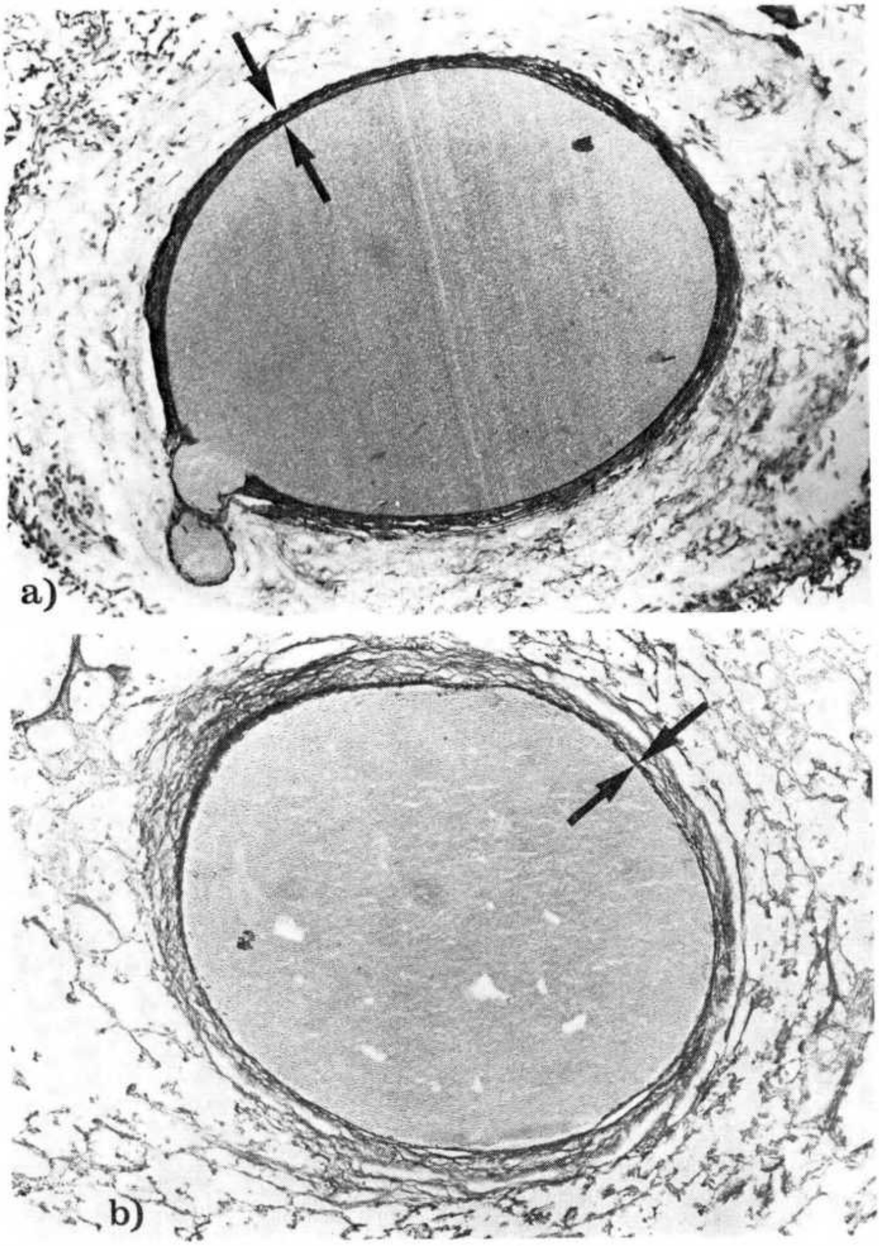

Fig. 4 *Photomicrographs of two peripheral pulmonary arteries of identical size from* (a) *an untreated case of pulmonary atresia and* (b) *a case of pulmonary atresia given PGE_1 for six days, showing the difference in thickness of the media between the arrows. (Original magnification × 414.)*

most susceptible to change, exaggerated the normal process of adaptation to extrauterine life. It is interesting to observe that in the normal child the plasma prostaglandin E concentrations are higher during the first 24 hours than at any other time of life, falling rapidly by the second and third day.[31]

By contrast, Manchester *et al.*[32] reported two infants born of mothers given the prostaglandin synthetase inhibitor, indomethacin, who experienced persistence of the fetal circulation, attributed to an abnormally high pulmonary vascular resistance, in the absence of a cardiac malformation or parenchymal lung disease. Indomethacin treated neonatal goats show an exaggerated response to hypoxia.[33] Levin *et al.*[34] reported an increase in pulmonary arterial medial width/external diameter ratio in two children born of mothers who took either salicylates or indomethacin during pregnancy. In one patient the ductus arteriosus remained patent, suggesting a direct effect of prostaglandin synthetase inhibitor on the pulmonary vascular smooth muscle, rather than the increased muscularity being secondary to premature closure of the ductus arteriosus.

Infusion of PGE_1 appeared to weaken the walls of muscular pulmonary arteries. This did not occur in untreated cases of pulmonary atresia, nor in a 15-day-old baby dying several days after a successful Waterston-Cooley anastomosis had been performed, but who had not received PGE_1.[10]

Infusion of PGE_1 also appeared to have a weakening effect on the wall of the ductus arteriosus in six of the seven cases in the present series in which the ductus was examined (A C Gittenberger-de Groot, 1979, personal communication). In four other babies there was 'oedema of the media with separation of medial components by clear spaces, pathological interruption of the internal elastic lamina and intimal laceration' after PGE_1 infusion,[35] changes similar to those found in the pulmonary arteries of the present series.

Table 3 *Arterial structural type related to external diameter*

Case no.	*Age at death (d)*	*Largest non-muscular (μm)*	*Range of partially muscular (μm)*	*Smallest muscular (μm)*
1	2	95·2	58·8–161	175
2	4	120·4	58·8–224	196
3	5	133·0	39·2–196	117·6
4	23	123·2	28·0–259	252
5	16	117·6	56·0–308	252
6	15	100·8	72·8–224	245
7	9	128·8	53·2–189	154
8	50	98·0	56·0–151·2	140
Normal[18]				
	3	152·0	40·0–180	120
	4 mth	130·0	40·0–170	175
	10 mth	125·0	55·0–220	112

Table 4 *Arterial structural type related to peripheral airway level*

Airway level	*Percentage of each type of vessel*		
	Normal	*Pulmonary atresia untreated*	*Pulmonary atresia given PGE_1*
Terminal brochioli			
Non-muscular artery	9·7	3·7	8·3
Partially muscular artery	66·3	88·0	91·7
Muscular artery	24·0	8·3	0
Respiratory bronchioli			
Non-muscular artery	43·0	41·2	56·6
Partially muscular artery	57·0	56·3	43·4
Muscular	0	2·5	0
Alveolar ducts			
Non-muscular artery	88·0	76·0	92·9
Partially muscular artery	12·0	24·0	7·1
Muscular artery	0	0	0
No. of cases	3*	7	7 (cases 1–7)

* Hislop.[19]

Microscopical examination showed widespread distension of the lymphatic channels in several cases. PGE_1 increases the permeability of small blood vessels in the skin, doing so at a dose as low as 50 ng, and in cremaster muscle.[36] Studies on the sensitised guinea-pig lung showed that release of PGE_1 from the lung was associated with leakage of fluid.[37] If PGE_1 does, indeed, increase the permeability of the small pulmonary vessels there are important clinical implications. In the normal lung, the rate of lymph clearance is higher during the first hours of life than at any other time as fetal lung fluid is cleared.[38] In pulmonary atresia, therefore, PGE_1 treatment would be better started after this time, if at all possible.

The present series of cases is too small to show whether or not there is a clear relation between dose, duration, and structural change. There was, however, a progressive reduction in muscularity the greater the duration of infusion in children started on PGE_1 during the first 24 hours of life (Fig. 3). The two cases receiving PGE_1 for the longest period of time had the most severe and widespread aneurysmal dilatation of muscular pulmonary arteries. In addition, children given PGE_1 for a similar length of time showed a similar structural response.

Several babies survived for some time after the PGE_1 infusion was stopped, raising the possibility that the structural changes seen at necropsy might not entirely represent the action of the drug. The structural findings in these babies did not, however, differ in kind from those found in infants dying while being infused with the drug. The most severe change occurred in three cases dying at between three and 13 days after stopping the infusion, suggesting that whatever change had been induced by the PGE_1 had either persisted or, indeed, had progressed after stopping the drug. The pulmonary blood flow probably never increased sufficiently in any patient to a point at which stimulation of vascular smooth muscle development might have occurred.

Case 8 showed less structural change than the other seven cases. This child might, however, have had a higher pulmonary blood flow and thus more pulmonary arterial muscle initially because treatment was not required until 40 days of age. At necropsy, the ductus arteriosus was relatively large and had the structural characteristics of a persistent ductus arteriosus rather than those of a normally closing ductus, as found in the six out of seven other cases examined (A C Gittenberger-de Groot, 1979, personal communication). In addition, starting treatment with PGE_1 at 40 days might produce less structural change than when started within the first hours of life.

CLINICAL IMPLICATIONS

Infusion of PGE_1 in babies with pulmonary atresia maintains the patency of the ductus arteriosus and ensures perfusion of the lung. In the present series, PGE_1 infusion was associated with dilatation of the preacinar arteries, a reduction in arterial muscularity, and an increase in number of intra-acinar pulmonary arteries. These effects are beneficial, since they are compatible with a reduction in pulmonary vascular resistance. Unfortunately, however, PGE_1 appears to have a weakening effect on the wall of muscular pulmonary arteries, an effect that may have been accentuated in these cases since pulmonary atresia is normally associated with a reduction in muscularity. Furthermore, the PGE_1 was generally used soon after birth when the pulmonary circulation is adapting most rapidly to extrauterine life, and, since adaptation is normally associated with a reduction in muscularity, the lung may have been particularly vulnerable to PGE_1 at this time. The pathological findings suggest that increased vascular permeability might be a second disquieting feature in the newborn infant.

The extent to which the structural changes in the muscular pulmonary arteries are reversible is unknown. Muscularity will, however, probably increase to a normal level given an increase in pulmonary arterial pressure and flow, just as muscularity increases abnormally in the presence of pulmonary hypertension.

Thus, the structural findings in the pulmonary circulation of children with pulmonary atresia treated with PGE_1 suggest that the drug is best started after the first few hours of life and given until the arterial oxygen tension is increased and the child's condition has improved sufficiently for him to undergo surgical treatment.

The reduction in arterial muscularity seen in the present series suggests that PGE_1 may have a wider application in the newborn period. In particular, it may be useful in the management of patients with a normal heart in whom pulmonary vascular resistance remains raised after birth and in children with congenital heart disease who are born with abnormally thick-walled muscular pulmonary arteries.

We wish to thank Professor W Gössner for allowing us to examine the necropsy specimens.

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Br Heart J 1980; **43:** 315–320

Intracardiac conduction defects in dystrophia myotonica

Electrophysiological study of 12 cases

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SUMMARY Twelve patients with dystrophia myotonica had cardiac electrophysiological study for conduction disturbances (five cases) or for syncope (seven cases).

Conduction disturbances were found in each case, being intranodal in two cases, intra-Hisian in three cases, or diffuse in seven cases. These findings are in agreement with those previously reported, and may be related to the high incidence of sudden death in these patients.

Pacemakers are advocated in symptomatic patients, and in some asymptomatic patients with severe and diffuse lesions.

Myotonic muscular dystrophy is a progressive autosomal dominant disorder[1] characterised by amyotrophy, especially obvious in the neck, face, and distal limb muscles, and widespread dystrophic change (cataracts, diabetes, hypogonadism, premature balding) which may be the result of an abnormality of the cell membrane[2] and myotonia.

The possibility of cardiac involvement was reported by Griffith[3] soon after Steinert[4] had defined the disease which sometimes bears his name. Many reports of electrocardiographic abnormalities followed and large series of patients studied by DeWind and Jones,[5] Fisch,[6] and Church[7] indicated the frequency of atrioventricular and intraventricular conduction defects. Independently, syncope from complete heart block, and sudden death were observed.[5 8 9] Complete heart block therefore seems to be the ultimate expression of a progressive conduction defect.[10 11]

The development of electrophysiological methods has allowed a more precise definition of the site of these abnormalities. The results obtained with these techniques in 12 patients with dystrophia myotonica are compared with those previously reported.

Subjects and methods

Twelve patients with dystrophia myotonica were referred by the Departments of Neurology of La Pitié-Salpêtrière Hospital for electrophysiological investigation between April 1973 and March 1978.

The indications for this investigation were either typical syncope or faintness associated with electrocardiographic abnormalities (seven cases), or asymptomatic conduction defects (five cases). The 12 patients comprised nine men and three women aged 18 to 69 years (average age 47 years).

The electrophysiological investigation was carried out using Scherlag *et al.*'s technique[12] with three bipolar USCI No 6 electrode wires introduced percutaneously via the femoral vein under local anaesthesia and without premedication. They were positioned in the upper right atrium, at the superior border of the tricuspid ring, and at the apex of the right ventricle. The recording was performed with a 6-channel Siemens ink-jet recorder at speeds of 50 and 100 mm/s.

The following intervals were measured in the basal state:

(a) PA: from the start of the P wave on the surface electrocardiogram to the intrinsic deflection of the atrial wave recorded on the atrioventricular lead (normal values (N): 40 ±15 ms).

(b) AH: from the intrinsic atrial deflection to the intrinsic deflection of the His potential (N: 70 ± 20 ms).

(c) H duration: (N: 15 to 20 ms).

(d) HV: from the intrinsic deflection of the His potential to the beginning of the ventricular depolarisation taken as the earliest ventricular event

Received for publication 27 April 1979

on either the V wave of the His bundle lead or the QRS on a surface electrocardiogram (N: 45 ± 10 ms).

Sinus function was tested by the extrastimulus technique[13] with measurement of the estimated sinuatrial conduction time (N: 200 ms) and by the corrected sinus node recovery time[14] (N: 500 ms).

Atrioventricular nodal conduction was assessed by measurement of the Wenckebach point, defined as the rate of right atrial pacing at which atrioventricular block is noted (N: 170 ± 20/min), and by measurement of the refractory periods by the extrastimulus technique.[15] The latter was performed in all patients except cases 2 and 6, for whom it was rendered impossible by supraventricular arrhythmias. The normal values[16] for pacing rate close to that of the sinus rhythm (600 to 750 ms) are given in Table 1.

Table 1

	Effective refractory period	*Functional refractory period*
A	235 ± 25	227 ± 33
AV	297 ± 20	388 ± 39
V	241 ± 21	265 ± 27

The sensitivity of the study of distal conduction was increased by the ajmaline test. This was performed in cases 1 to 6 using an intravenous injection of 50 mg ajmaline over 1 minute followed by a second injection of 50 mg 5 minutes later; in cases 7 to 12 ajmaline 1 mg/kg body weight was injected at a rate of 1 mg/s. The test was considered positive if the HV interval exceeded 100 per cent of its initial value or exceeded 90 ms.[17]

The investigation was performed after withdrawal of all treatment (quinidine, procainamide, phenytoin) which might have modified the values being measured. In case 8 the His potential was also recorded externally during follow-up by signal averaging[18] and summation after suitable amplification, using a PDP 11/20 mini-computer (Fig. 1). In cases 2 and 6 conduction was assessed by RR interval histogram because of atrial arrhythmias (Fig. 2).

Results

These are shown in Table 2. On the surface electrocardiogram, abnormalities were found in all subjects except case 11. First-degree heart block was very frequent, being seen in 9, either as an isolated finding in three or associated with intraventricular conduction defects in six. In the presence of supraventricular arrhythmias (cases 2 and 6) atrioventricular conduction was delayed: atrial flutter was conducted either 4:1 or 6:1, and in atrial fibrillation the ventricular cycle length ranged from 600 to 1600 ms. Intraventricular conduction disturbance was more commonly left-sided (four with left bundle-branch block, one with pronounced left axis deviation), than right-sided (three with right bundle-branch block). These abnormalities may become more severe with time; with observations made over a period of six months

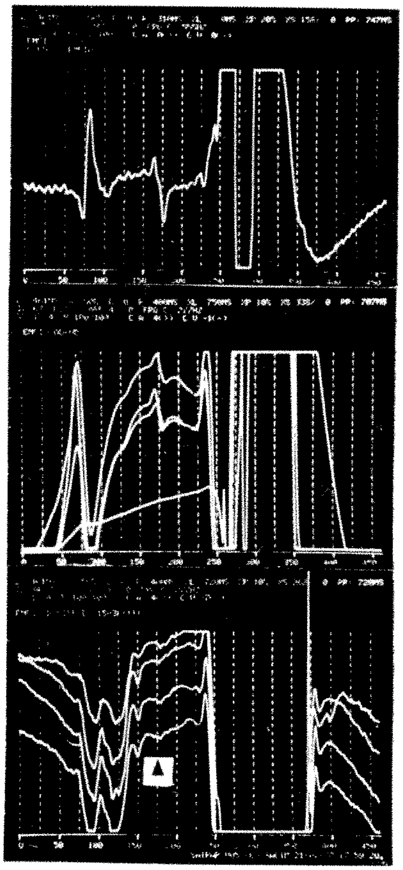

Fig. 1 *Case 8. Display of analogue signals on the computer terminal. Scale is 50 ms between each vertical dotted line.*
Top tracing: *A, H, and V recordings by normal bipolar endocardial catheter.* Middle tracing: *A, H, and V recordings by bipolar catheter with widely separated electrodes (right atrium, right ventricular apex).*
Bottom tracing: *external recordings with digital signal averaging. Each trace is averaged from 100 cycles. The first wave is the amplified and averaged P wave. The arrow points out a wave synchronous to the His bundle recording, between the P and the averaged QRS. The same pattern is found for each averaged series.*

to 10 years, the PR interval was seen to lengthen in four cases (cases 1, 7, 8, and 10) and the QRS complexes to widen in four (cases 2, 7, 8, and 10).

Electrophysiological investigation showed sinus node function to be normal in all eight patients in whom it was studied (cases 3, 4, 5, 8, 9, 10, 11, and 12). The intra-atrial conduction as measured by the PA interval was normal in the 10 cases in which it could be measured, but the intra-atrial conduction refractory period was increased in cases 1, 5, 9, 10, 11, and 12. The intranodal conduction time (AH interval) was recorded in 10 cases and increased by 80 to 285 per cent in cases 1, 3, 4, 5, 7, 9, and 12, thus demonstrating block proximal to the bundle of His. The Wenckebach point produced by intranodal block was observed at pacing rates of 100/minute or less in cases 1, 3, 7, and 9. The effective atrioventricular conduction refractory period was increased in cases 1, 3, 5, 7, 9, and 11 (Fig. 3). The functional atrioventricular conduction refractory period was increased in cases 3, 4, 7, and 9. A supraventricular arrhythmia prevented the recording of the refractory periods in two patients but the slow ventricular rhythm in these cases suggested an intranodal conduction defect. Conduction delays at the atrioventricular node were thus observed in nine of 12 patients.

Conduction within the bundle of His was abnormal in cases 5 and 11. First degree bundle-branch block was recorded with widening of the

Table 2 *Results in 12 patients*

Case no. sex, age (y)			*Symptoms*	*ECG*	*Intervals (ms)*			*Wenckebach phenomenon (rate/min)*		*ERP (ms)*	*FRP (ms)*	*Ajmaline test*	*Conduction defects*	*Necropsy*
					AH	*H*	*HV*							
1	M	50		PR = 260	150	15	55	90	A AV V	300 400 160	240 380 200	+	Nodal + distal	–
2	M	69	Faintness	AF, LAD		10	50	—	A AV V	— — —	— — —	+	Nodal + distal	+
3	M	33	Faintness	PR = 240	150	15	35	90	A AV V	220 580 260	200 440 240	–	Nodal	–
4	M	23		PR = 240, RBBB	125	15	70	140	A AV V	220 520 320	200 300 240	+	Nodal + distal	+
5	M	56		PR = 220, LBBB	130	40	60	130	A AV V	320 380 240	360 440 300	+	Nodal + intra-Hisian + distal	+
6	F	52	Faintness	Flutter, LBBB	—	10	40	—	A AV V	— — 320	— — 360	+	Nodal + distal	+
7	F	58	Syncope	PR = 380, RBBB	270	10	60	95	A AV V	— 590 300	— 670 280		Nodal + distal	+
8	M	54		PR = 200, LBBB	95	10	60	160	A AV V	260 420 —	240 260 —	+	Distal	–
9	M	52	Syncope	PR = 240	140	15	55	100	A AV V	280 440 280	260 760 225	+	Nodal + distal	+
10	F	48		PR = 220, LBBB	80	10	55	160	A AV V	305 380 300	220 205 250	+	Distal	–
11	M	18	Syncope	Normal	40	20	50	150	A AV V	278 396 300	294 358 260	–	Intra-Hisian	+
12	M	53	Faintness	PR = 240, RBBB	190	15	40	160	A AV V	280 360 260	260 300 240	–	Nodal	–

LAD, Left axis deviation; LBBB, left bundle-branch block; RBBB, right bundle-branch block; AF, atrial fibrillation; ERP, effective refractory period; FRP, functional refractory period.

His potential, which was split after an extrastimulus in case 11. A distal conduction defect with lengthening of the HV interval was observed in 9 of 12 cases, either without drugs (cases 4, 5, 7, and 8) (60 to 70 ms) or after ajmaline (cases 1, 2, 6, 9, and 10) when it increased by more than 100 per cent. Refractory period of intraventricular conduction was increased in cases 6 and 7.

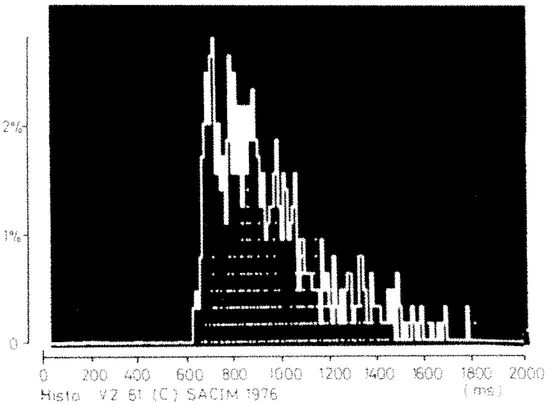

Fig. 2 *RR interval histogram of case 2. Periods range from 600 to 2000 ms.*

There was little correlation between electrophysiological findings and the symptomatology as severe intra- and infra-Hisian conduction defects were observed both in patients with typical syncopal attacks (cases 7, 9, and 11), in patients with atypical symptoms (cases 1 and 6), and in asymptomatic patients with electrocardiographical abnormalities (cases 2, 4, 5, 8, and 10).

Discussion

Electrocardiographic abnormalities are very frequent in myotonica dystrophia. DeWind and Jones[5] reported an incidence of 62 per cent in a series of 98 cases, and Church[7] 85 per cent in 236 cases. In some cases, low voltage P waves or supraventricular arrhythmias are observed, atrial flutter more often than atrial fibrillation, associated with slow ventricular rhythms.[19 20] However, atrioventricular and intraventricular conduction defects predominate and are the object of this study: first degree atrioventricular block is reported in approximately 40 per cent of cases already published (Table 3) and in nine of 12 cases in our series. Higher degrees of atrioventricular block[6 21 22] or complete heart block[5 10 23] have also been reported but were not observed in our series. Intraventricular conduction defects have been seen nearly as often (Table 4) associated with long PR intervals in half the cases.

Table 3 *Incidence of first degree atrioventricular block*

Authors	*No.*	*Abnormal*	*Per cent*
Church[7]	236	89	38
DeWind and Jones[5]	98	42	43
Fisch[3]	85	41	48

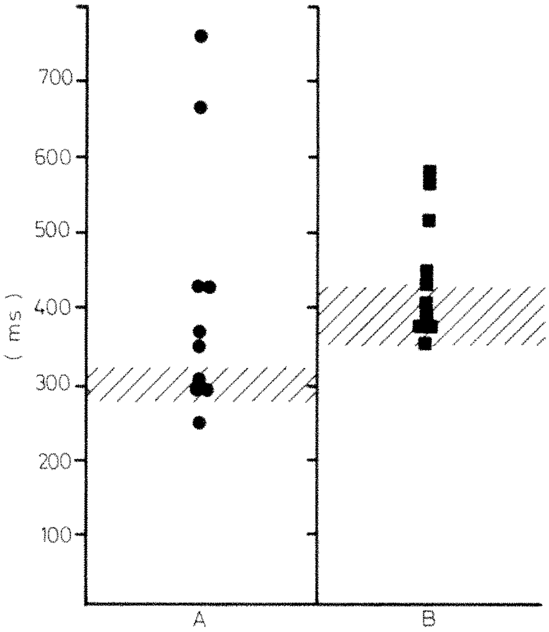

Fig. 3 *Effective refractory periods* (A) *and functional refractory periods* (B) *of atrioventricular conduction in 10 patients. Mean values (normal): ERP: 297 ± 20 ms; FRP: 388 ± 39 ms.*

Table 4 *Incidence of intraventricular conduction defects*

Authors	*No.*	*RBBB*	—	*LBBB*	*LAHB*
Church[7]	236		32 (14%)		45 (19%)
Fearrington *et al.*[19]	17	1 (6%)		3 (18%)	
Laurent[20]	138	13 (9%)		18 (13%)	22 (16%)
Schmitt *et al.*[25]	13	2 (15%)		2 (15%)	3 (23%)
Welsh *et al.*[27]	34	5 (14%)		6 (18%)	8 (24%)

LAHB, left anterior hemiblock.

In a review of the existing literature, 33 cases of dystrophia myotonica were found with documented electrophysiological investigations comprising basal AH and HV intervals (Table 5), sometimes with mention of the Wenckebach point,[22 24 25] and in one case with the ajmaline test.[22] This series included 20 instances of atrioventricular block and 15 of intraventricular conduction defects, associated with atrioventricular block in 13 cases.

The indications for electrophysiological investigation were given in only 18 cases; five were for symptoms and 13 were systematic investigation. The authors reported six isolated nodal blocks, seven isolated distal blocks, and 12 multilevel blocks.

Table 5 *Electrophysiological studies in dystrophia myotonica*

Authors	*No. of cases*
Griggs *et al.*[24]	11
Josephson *et al.*[21]	2
Leprat[22]	3
Meihac *et al.*[30]	1
Montoyo *et al.*[31]	4
Schmitt *et al.*[25]	8
Thery *et al.*[28]	1
Uemura *et al.*[32]	3

This is in keeping with our results where conduction defects were sometimes isolated (two nodal blocks, one bundle-branch block, two infra-Hisian blocks), and in general diffuse, multilevel (seven cases) involving the atrioventricular node, the His bundle, and the bundle-branches. It confirms the predominance of widespread involvement of the atrioventricular conduction pathways in dystrophia myotonica; combined experience is reflected in Fig. 4.

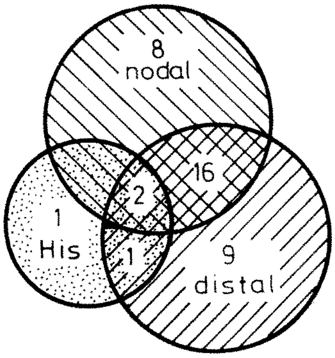

Fig. 4 *Atrioventricular conduction defects in 37 patients with dystrophia myotonica, according to the site of conduction disturbances (nodal, His bundle, distal).*

Severe conduction defects are observed in two out of three investigations, but this reflects a group of patients who were either symptomatic or had abnormal electrocardiograms; the incidence is therefore higher than it would be in an unselected series. With this reservation, certain conclusions can be drawn as to the management of conduction defects in these patients.

The symptomatology may be unreliable for, though typical syncopal attacks are always associated with high-degree distal blocks, two asymptomatic patients were found to have multilevel block (surface electrocardiogram: first degree block) and a distal block (electrocardiogram normal). The surface electrocardiogram does not always provide full information: 36 abnormal electrocardiograms showed distal (in nine cases) or multilevel (in 18 cases) bundle-blocks in 75% instances. Among these cases distal conduction defects were observed in six of 10 patients with first degree block but narrow QRS complexes, and thus surface electrocardiograms which were more suggestive of simple delay of nodal conduction. Bundle-block and distal block were each discovered once among the nine remaining cases with normal electrocardiograms.

The evolution of these lesions is variable. The progressive deterioration of the conduction defects observed in our series is in accord with previous reports of the appearance[11] or aggravation of atrioventricular block,[8 10 21] or bundle-branch block, usually left-sided.[10 11]

Sudden death may result from complete heart block[8 9]; this may cause death in perhaps 10 per cent of cases.[26] Conversely, the stability of lesions as observed on the surface electrocardiogram has been the subject of other reports.[11 27]

The management of these patients is difficult in view of the unknown natural history of the conduction defects in the absence of repeated electrophysiological investigation on a large series of patients, and in view of the rarity of histological studies of the conduction pathways which may be affected at all levels[28 29] In previous publications permanent pacing was reserved for all patients with a history typical or suggestive of Adams-Stokes syncope.[10 21 23] Our attitude is slightly different. pacemakers are implanted in all patients with a typical or suggestive history of syncope with multilevel or distal conduction defects. On the other hand, a wait-and-see attitude is adopted for asymptomatic patients despite the presence of distal or multilevel conduction defects. Non-invasive His bundle recording, when possible, may be used for the follow-up of such patients, as in one of our cases. The implantation of a pacemaker is, however, recommended to prevent iatrogenic aggravation of conduction defects in patients on drugs known to depress the conduction distal to the bundle of His, such as quinidine and procainamide.

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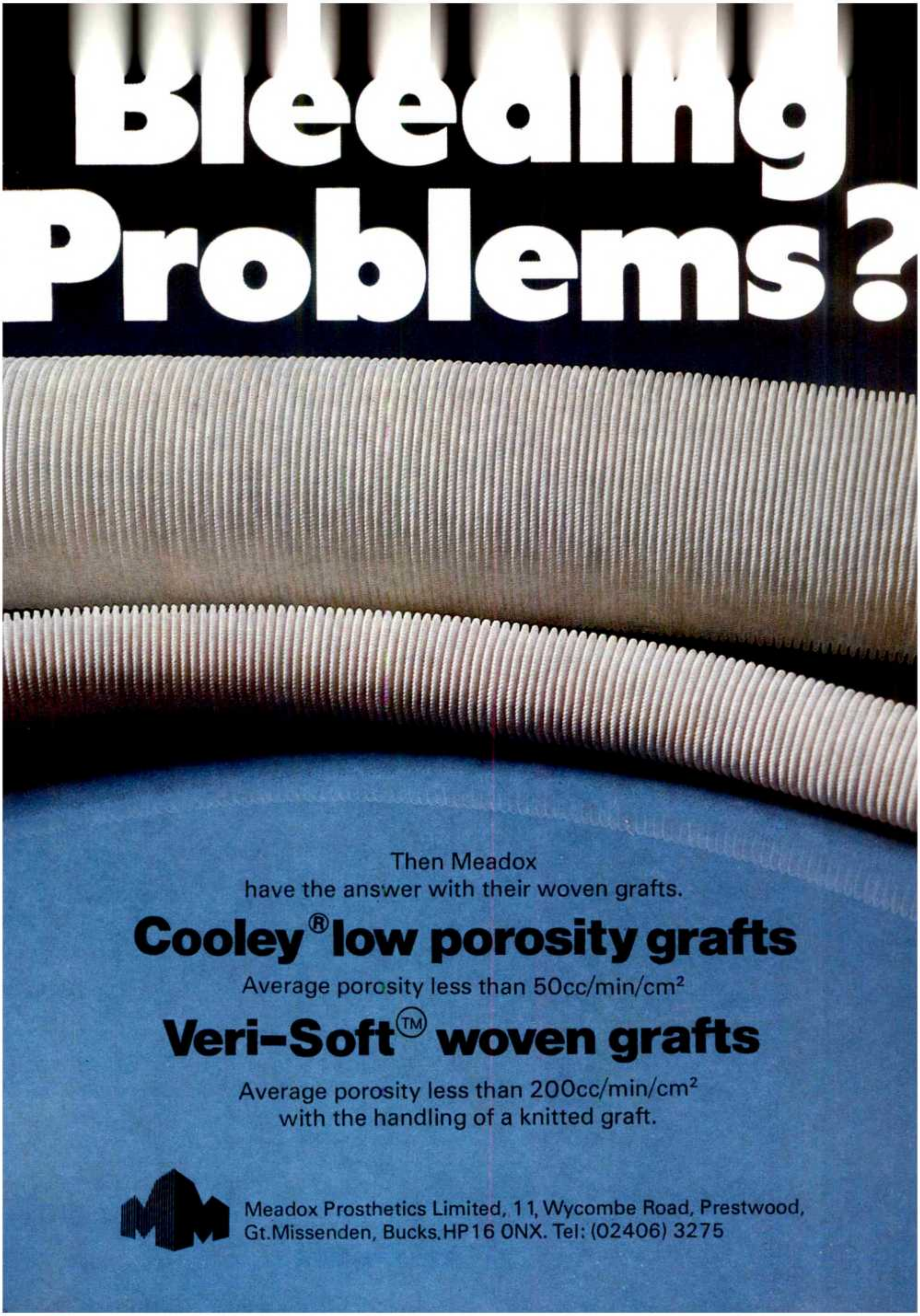

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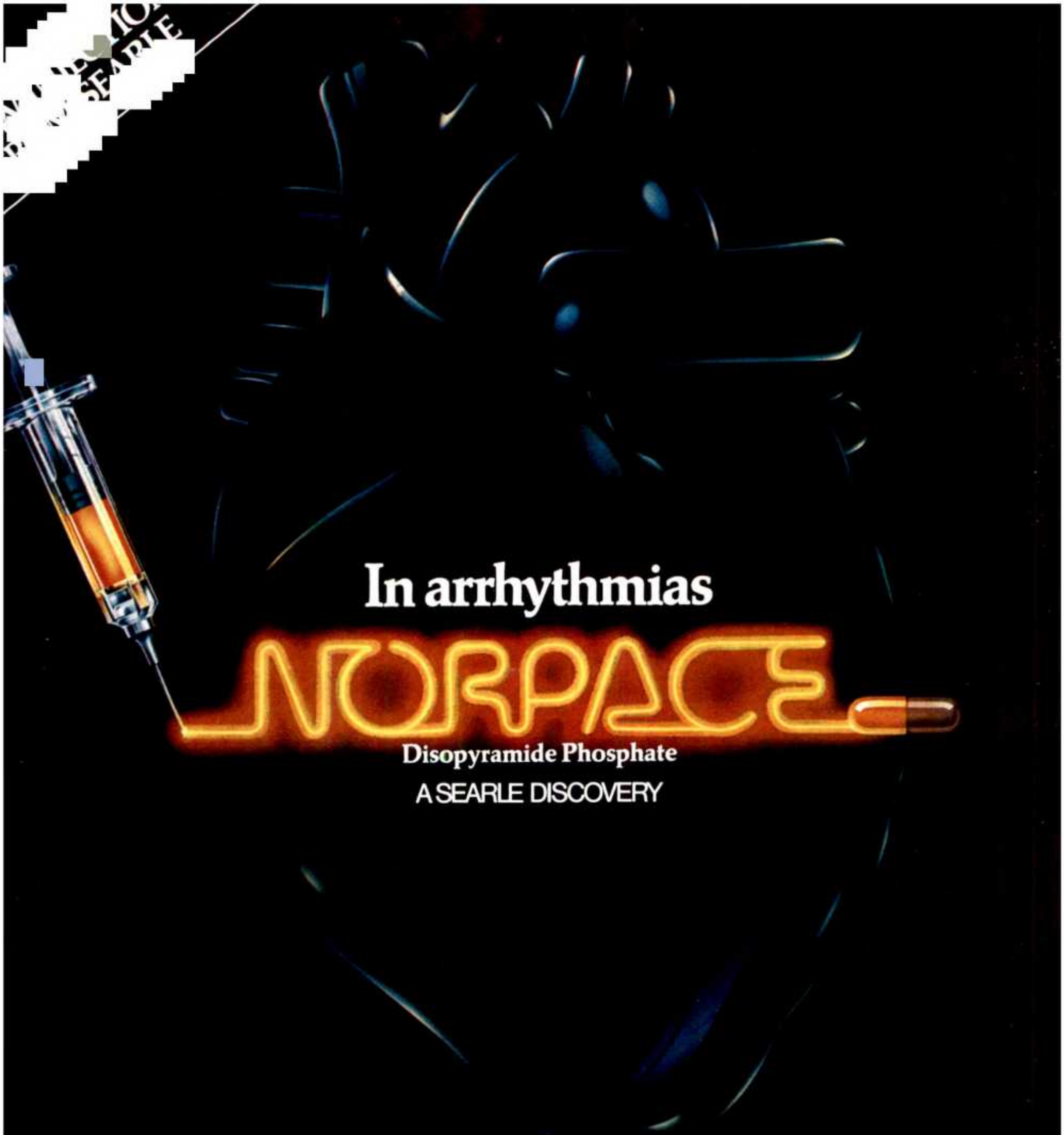

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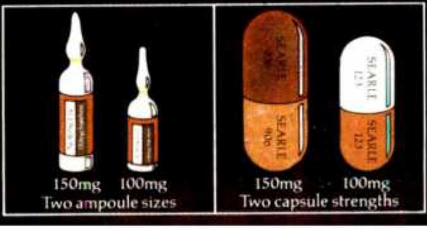

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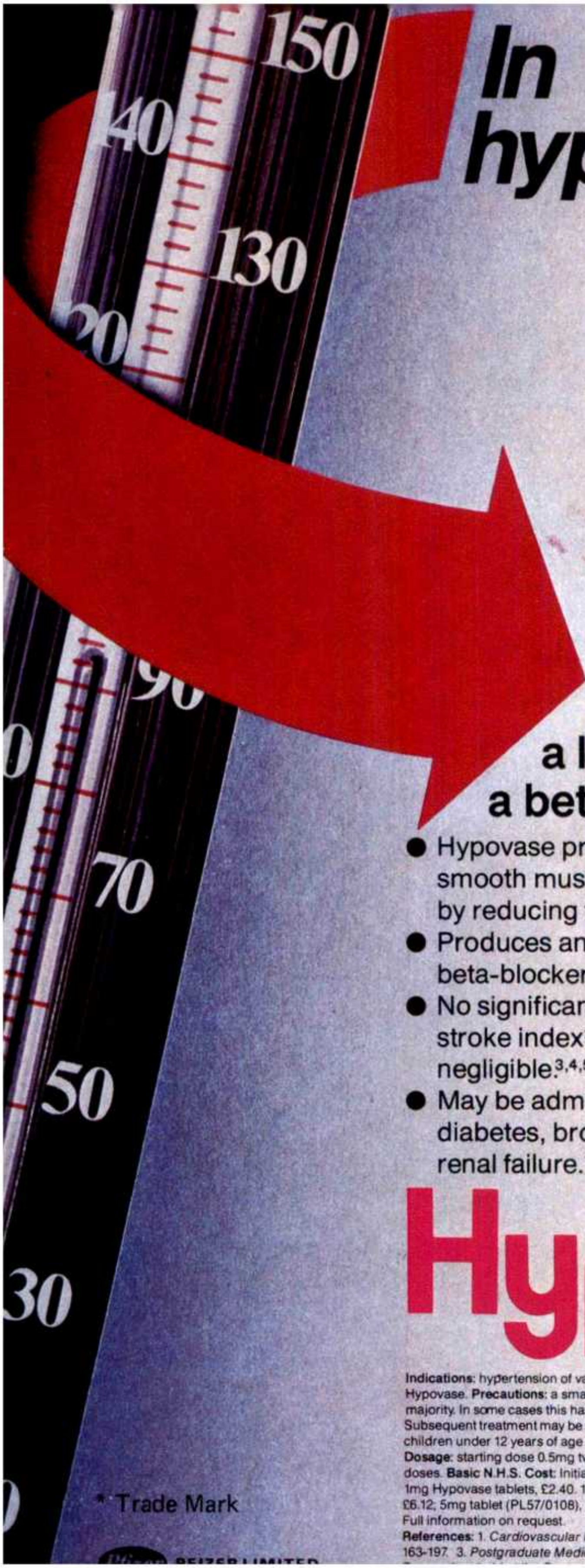

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Permanent cardiac pacing using anterior pectoral veins

A G ARNOLD

From the Department of Cardiology, John Radcliffe Hospital, Headington, Oxford

SUMMARY We have used the anterior pectoral veins for inserting permanent transvenous cardiac pacemaker electrodes in 260 patients. Though this route is used in other centres it has not been published. We found it to be a reliable alternative to the more usual routes of pacemaker insertion, with a combined perforation and displacement rate of 9·6 per cent. We describe this technique of electrode insertion and compare the complication rates with those of other routes of implantation used in our department. All of the pacemaker implantations in this study were performed by doctors in the cardiology department, with no specialist surgical training.

The annual rate of new pacemaker implantations in Britain is still increasing, and the rate for 1980 has been predicted as 150 per million of the population.[1] The majority of these pacemaker implantations use the transvenous route rather than an epicardial route. Though the external jugular vein and axillary vein[2] are sometimes used for electrode insertion, the cephalic vein is the commonest transvenous route.[1] Technical difficulties can arise with these routes, and in a variable proportion of patients the cephalic vein cannot be used. A more recent study described the use of direct subclavian vein puncture, but only in a group of 40 patients.[3]

We describe a method which uses the anterior pectoral veins and compare our experience with this method with those other routes of electrode insertion.

Subjects and methods

We retrospectively analysed the records of all patients who had permanent cardiac pacemakers implanted between January 1975 and March 1979, regardless of the indication for pacing. The minimum period of follow-up was three months. Particular attention was paid to the complications of electrode displacement and myocardial perforation. In cases of repeated displacement each event was documented separately.

When the cephalic or subclavian routes were used the procedure was as previously described.[3] If the anterior pectoral vein is used an incision is made midway between the axilla and the mid-point of the clavicle (Fig. 1), of approximately 10 cm in length, after local anaesthetic infiltration. This incision is deep enough to expose the anterior surface of pectoralis major and crosses the line of cleavage between its sternal and clavicular heads. These two heads are separated by blunt dissection to

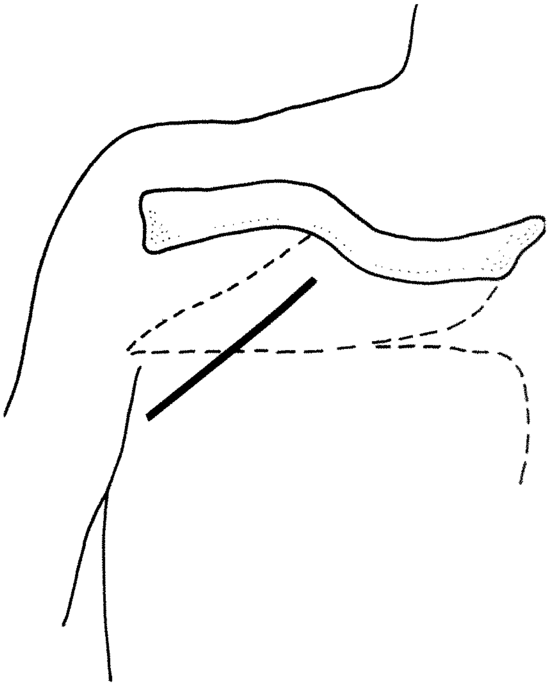

Fig. 1 *Line of incision in relation to surface anatomy, and two heads of pectoralis muscle.*

Received for publication 22 August 1979

expose an underlying layer of adipose tissue, crossed by the anterior pectoral veins in a neurovascular bundle. Separation of the muscle heads is eased by further local anaesthetic infiltration. A self-retaining retractor is then used to allow the vein to be dissected towards the subclavian vein, beneath the clavicular portion of pectoralis major, to a point where the calibre of the vein permits electrode insertion (Fig. 2). Underslung ties and an introducer make electrode insertion simpler, and the electrode then passes easily to the right atrium. The electrode is positioned in the right ventricle according to the radiological position of the electrode, the voltage threshold, and the intracardiac electrogram. When a stable position is found the electrode is first secured to the vein, and then to the surrounding fascia, by non-absorbable silk sutures. A subcutaneous pouch is fashioned superficial to pectoralis major to accommodate the generator unit.

Small surface area, non-wedged electrodes were used for subclavian vein insertion. With other routes of insertion large surface area and wedge electrodes were also used. There were two basic endocardial unipolar electrode types used in the study (Devices SC62 and LEM A7602), though some of the LEM electrodes differed in their tip dimensions (A7602B, A8603, and A8603B).

Results

The results of all three routes of transvenous pacemaker insertion are listed (Table). Electrode displacement and myocardial perforation are grouped together because of the difficulty occasionally in differentiating between these two complications.

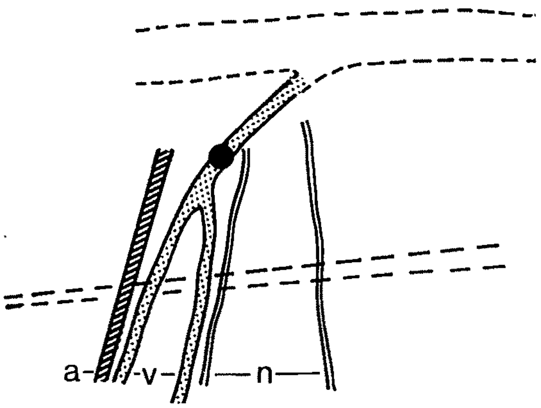

Fig. 2 *Neurovascular bundle beneath pectoralis major. The large dot indicates the point of electrode insertion. a, artery (thoracic branch of thoraco-acromial artery); v, vein (anterior pectoral vein); n, nerve (medial and lateral branches of the pectoral nerve).*

Table *Complications of transvenous pacemaker insertion*

	Route of insertion			
	Anterior pectoral vein	*Subclavian vein*	*Cephalic vein*	*Total*
Uncomplicated cases	235	61	151	447
Displacement and perforation (No.)	25	16	23	64
Displacement and perforation (%)	9·6	20·78	13·22	12·5
Total	260	77	174	511
p	0·02	NS		
		NS		

Other complications such as a rise in threshold, infection, and electrode fracture occurred in eight per cent of our whole group, but were evenly distributed between the three routes of insertion. In addition, axillary vein thrombosis occurred in three patients, all in the cephalic vein group. One patient sustained a large pneumothorax as a result of use of the subclavian vein route. These complications did not follow use of the anterior pectoral vein.

Although insertion of an electrode via the anterior pectoral vein meant that the electrode was placed through the muscle layer, neither impaired motor activity nor discomfort were noted.

The results of pacemaker electrode insertion were analysed by the χ^2 test with Yates's correction.

Discussion

The commonest complication of permanent cardiac pacemaker insertion is electrode displacement, and this usually occurs in the first 48 hours after insertion[4] and occasionally up to three months afterwards.[5] Several series have shown displacement rates of 0 to 40 per cent,[6-8] but the average rate in this country is 10 per cent.[1] There are two main reasons why electrodes displace, the first being the amount of slack left in the atrium, which can be too much or too little; the second is traction on the proximal portion of the electrode.[4]

Pacemaker electrode perforation of the right ventricle can be fatal[9] because of tamponade, but more often presents as pacemaker malfunctioning, and requires a further operation for repositioning.[10-12] The documented rate of perforation has varied between 2 and 7 per cent in several series.[5 12 13] Though physical examination and chest radiographs are of little help in diagnosing this, the intracardiac electrogram can be of assistance.[9] In practice, when faced with pacemaker malfunction, it may be difficult to differentiate between electrode perforation and displacement. In either case the electrode must be repositioned or replaced, and this difficulty might account for the varying perforation rates that have been reported.

If the point of electrode insertion into the vein is too close to the shoulder joint skeletal movement may cause traction on the electrode, and predispose to displacement. This may be the reason why cephalic vein insertion was less successful than anterior pectoral vein pacing in our study, and might account for the relatively high displacement rate when the axillary vein was used.[2] The cephalic vein cannot be used in 5 to 20 per cent of patients because of venospasm or anatomical variations.[5 13]

If the subclavian puncture method is used many additional complications may be encountered, such as pneumothorax,[14] arteriovenous fistula,[15] air embolism,[16] and phrenic nerve damage,[17] though they are likely to be rare if the subclavicular approach is used. Pneumothorax occurred as a complication in one of our cases of subclavian puncture. Our complication rate was higher than the earlier study,[3] but the rate was artificially low in that study since the number of patients with displacement, not the total number of displacement events, was recorded. We suspect that our complication rate was higher with this route because the electrode cannot be secured directly to the vein, but only to the fascia. This could make the electrode more prone to traction. With the subclavian route of insertion it can be difficult to insert large or wedge-tipped electrodes because of insufficient space between the clavicle and the first rib.[3]

The anterior pectoral vein route involves more dissection than alternative routes and tends to be a longer procedure. Separation of the muscle bellies can be uncomfortable unless adequate local anaesthesia is used. Occasionally the anterior pectoral veins are too small to be used, and alternatives have to be sought. Similarly, the cephalic and subclavian routes cannot always be used. This might be because the vein cannot be located, or because an electrode will not pass along the vein easily, though the vein can be entered. In this situation it is helpful to be able to use alternative routes, and we have found the anterior pectoral vein of value. Our complication rate was the lowest in the anterior pectoral vein group, and the difference between the complication rate in this group and the subclavian group satisfied standard tests of statistical significance.

In our total group of patients two main types of electrode were used, with similar complication rates for each. A further type of electrode was withdrawn from use because of an unacceptably high complication rate, and was therefore excluded from our study. Only experienced operators were used since the experience of the operator can obviously influence the rate of displacement.[18] Similarly, increasing experience of a particular transvenous route improves the results, and our own results seem to support this.

In this study we describe the use of the anterior pectoral vein as a route for the insertion of permanent pacemaker electrodes. Our results suggest that this is a safe method which appears to be at least as effective as other routes previously described.

I am grateful to Mr H F M Bassett of Manchester Royal Infirmary for permission to report a technique that he first devised and to Professor P Sleight for his helpful advice.

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Br Heart J 1980; **43:** 325–331

Echophonocardiography in diagnosis of mitral paravalvular regurgitation with Björk-Shiley prosthetic valve

B EDMUND GRIFFITHS, RICHARD CHARLES, NORMAN COULSHED

From Liverpool Regional Cardiac Centre, Sefton General Hospital, Liverpool

SUMMARY The echophonocardiographic features in three patients with a mitral Björk-Shiley prosthesis and paravalvular regurgitation are presented. The characteristic features are an early diastolic humping of the Björk-Shiley disc echo, associated with normal rather than paradoxical septal motion, and a reduced A2-MVO interval. The diagnosis was confirmed at operation in one patient, at cardiac catheterisation and operation in the second, and at necropsy in the third. These features were abolished by surgical correction of the leak in both operated cases.

Haemodynamic deterioration in patients with prosthetic heart valves may be rapid and severe but its precise cause may be obscure without resort to full cardiac catheterisation. Since many of these patients may be acutely ill, it is clearly desirable to be able to make a non-invasive assessment of the cause. The echophonocardiographic abnormalities caused by mechanical dysfunction of a variety of ball and disc valves have been described.[1 2] With the increasing use of the Björk-Shiley prosthetic valve, the echocardiographic appearances of the normally functioning valve have been described,[3 4] but its assessment is more difficult because of the spatial asymmetry of the disc and the variable orientation of the valve according to the method of insertion. Nevertheless, echocardiographic abnormalities caused by dysfunction of the Björk-Shiley valve in the aortic[5] and mitral[6] positions have been reported, the latter authors describing a study of two patients with valve obstruction and two patients with paravalvular regurgitation.

We present a combined echophonocardiographic study of three patients with paravalvular regurgitation, which confirms the echocardiographic findings of Bernal-Ramirez and Phillips[6] and shows also that they are associated with a reduced interval between the aortic second sound and mitral valve opening (A2-MVO) as previously described for other prosthetic valves.

Subjects and methods

The echocardiograms were obtained with a Smith Kline ultrasonoscope using a 2·25 MHz transducer (1·5 cm diameter). Permanent recordings were obtained at paper speeds of 50 and 200 mm/s, using a Cambridge strip chart recorder. The echocardiograms were obtained with the patients in a slightly left lateral position, with the head and thorax raised at 20°. The transducer was positioned in the third or fourth left intercostal spaces and directed towards the prosthetic mitral valve to record maximal excursion of the tilting disc. Further echocardiograms were obtained of the aorta and left atrium and of the body of the left ventricle below the prosthetic mitral valve. Echophonocardiograms recorded at 200 mm/s were used to measure the interval between the first high-frequency component of the second heart sound and peak opening of the prosthetic valve (A2-MVO interval), and the opening and closing velocities of the Björk-Shiley valve echo. Values greater than 180 and 300 mm/s were accepted as normal for opening and closing velocities, respectively[6]; the normal A2-MVO interval for a tilting disc prosthesis (Lillehei-Kaster) was taken as 90 ±10 ms.[2]

Received for publication 30 July 1979

Case reports

CASE 1

A 40-year-old woman with rheumatic heart disease underwent mitral valve replacement with a 29 mm Björk-Shiley prosthesis in January 1978. Her immediate postoperative course was complicated by an embolic occlusion of the right ilio-femoral artery necessitating emergency embolectomy; an organised clot, sterile on culture, was removed from

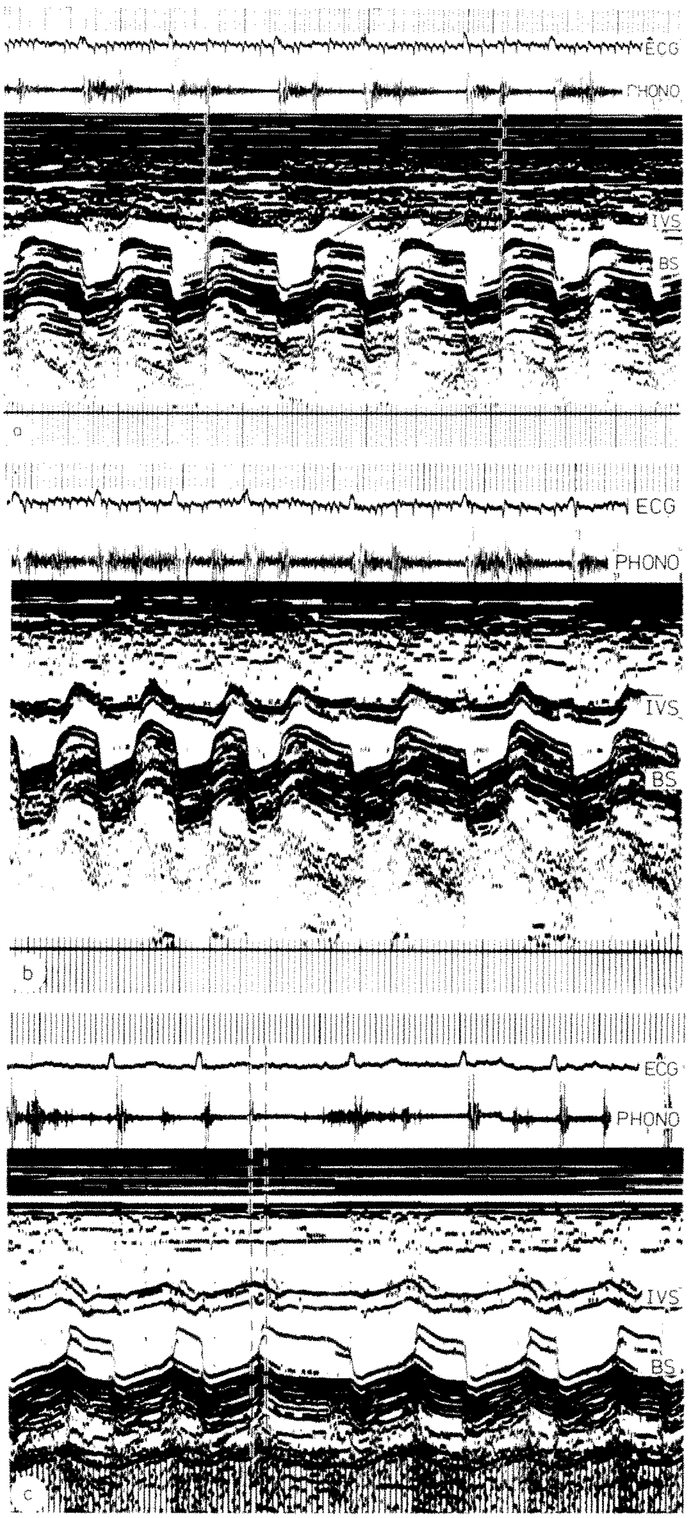

Fig. 1 *(Case 1)* (a) *Echophonocardiogram showing a reduced A2-MVO interval of 35 ms and normal opening and closing rates of 500 and 700 mm/s, respectively. The abnormal early diastolic hump is indicated by the arrows. The dotted lines in this and subsequent figures indicate the aortic second sound and the point of maximal prosthetic disc opening. The time lines indicate an interval of 40 ms. All recordings shown were made at a paper speed of 50 mm/s but measurement of A2-MVO interval and disc velocity were made from recordings at 200 mm/s (not illustrated); normal values: opening velocity > 180 mm/s, closing velocity > 300 mm/s; A2-MVO interval 90 ± 10 ms. BS, Björk-Shiley mitral prosthesis.* (b) *During shorter RR intervals the whole Björk-Shiley valve diastolic slope is rounded anteriorly rather than having the normal variable downward slope. Septal motion is normal rather than paradoxical.* (c) *Postoperative echophonocardiogram. A2-MVO interval 100 ms. Loss of early diastolic hump and return of normal diastolic slope of the Björk-Shiley valve echo. Return of paradoxical septal motion.*

the common iliac artery. On the twentieth postoperative day, she developed pulmonary oedema and was re-admitted to hospital from convalescence. She was critically ill, grossly orthopnoeic, and febrile but with no stigmata of bacterial endocarditis. Clear opening and closing clicks of the Björk-Shiley valve were heard and there was a faint mid-diastolic murmur at the cardiac apex, but there was no audible pansystolic murmur.

The electrocardiogram showed uncontrolled atrial fibrillation and the chest radiograph confirmed pulmonary oedema. The echophonocardiogram is shown in Fig. 1a and 1b. The Björk-Shiley valve has normal opening and closing velocities, normal amplitude of movement, but an intermittent rounded early diastolic humping of the Björk-Shiley valve is seen, together with an abnormal diastolic slope in the shorter RR intervals. The phonocardiogram shows an A2-MVO interval of 35 ms and septal motion is normal rather than paradoxical. At emergency operation the next day the mitral prosthesis was found to be detached anteriorly by about 1·5 cm, and several granulations were seen on the valve ring. The valve was excised and a new 29 mm Björk-Shiley valve was sutured in its place.

Staphylococcus albus was cultured from the excised valve and a six-week course of streptomycin and benzylpenicillin resulted in a full clinical and radiological recovery.

The postoperative echophonocardiogram is shown in Fig. 1c. This shows loss of the early diastolic humping, restoration to normal of the Björk-Shiley valve diastolic slope and of the A2-MVO interval (100 ms), and return of paradoxical septal movement.

CASE 2

A 44-year-old woman underwent closed mitral valvotomy for rheumatic mitral stenosis in January 1978. Unfortunately, she developed significant mitral regurgitation and in February 1978 the diseased mitral valve was replaced with a 31 mm Björk-Shiley prosthetic mitral valve.

Her immediate postoperative period was complicated by the development of a left hemiparesis, but there was rapid and almost total recovery of function within a few days. By the time of her discharge she was well, with a clinically competent prosthetic mitral valve. Three months after operation she was re-admitted with a seven-day history of nausea, vomiting, dyspnoea, and orthopnoea. On admission, she was clearly ill with congestive failure and tricuspid regurgitation. The pulse was irregular, 100/min with runs of bigeminal rhythm, and jugular venous pressure was raised to 10 cm, with dominant *cv* waves and rapid *y* descent. A loud pansystolic murmur was loudest at the tricuspid area but was heard faintly at the mitral area and in the axilla, and normal opening and closing clicks of the prosthetic mitral valve were present. There were widespread basal crepitations and the liver was enlarged and pulsatile.

The electrocardiogram on admission suggested digoxin toxicity and the chest *x*-ray film confirmed pulmonary oedema. The serum digoxin level was 4·3 nmol/l. Her condition rapidly improved with increasing diuretic therapy and temporary discontinuance of digoxin, with disappearance of the signs of tricuspid regurgitation and clearing of the chest *x*-ray film. However, a soft pansystolic murmur remained at the axilla.

The echophonocardiogram shortly after admission is shown in Fig. 2a. The essential findings are the normal opening and closing velocities and amplitude of excursion of the Björk-Shiley valve, but a short A2-MVO interval of 55 ms, normal rather than paradoxical septal movement, and early diastolic humping of the Björk-Shiley mitral valve. The other echocardiographic views in this case show a dilated left ventricular cavity with a vigorously contracting posterior left ventricular wall (Fig. 2b) and a dilated left atrium with systolic expansion of the left atrial wall in the region of the aortic valve (Fig. 2c).

In view of these findings, cardiac catheterisation was performed. The mean left atrial pressure was 27 mmHg, with a *v* wave of 50 mmHg rising to 70 mmHg after angiocardiography. Left ventriculography confirmed severe regurgitation around the Björk-Shiley prosthesis into an enlarged left atrium. At operation, the Björk-Shiley prosthesis looked normal. There was no cloth wear and the disc functioned normally. There was a tear 0·5 cm lateral to the valve corresponding to about one-sixth of the circumference of the sewing ring. All the suture material was intact and there was a rim of tissue attached to the sewing ring in this area.

The paraprosthetic leak was thus a result of tissue failure and tearing. This defect was closed using a series of interrupted and continuous sutures through the cardiac tissue approximating it to the valve ring, and the heart was defibrillated to sinus rhythm. The postoperative echophonocardiogram is shown in Fig. 2d. The diastolic slope of the Björk-Shiley valve is now normal, with loss of the early diastolic hump, and the A2-MVO interval is 120 ms. A mid-cavity view confirmed the return of paradoxical septal motion.

CASE 3

A 68-year-old woman underwent tricuspid valvotomy and mitral valve replacement with a

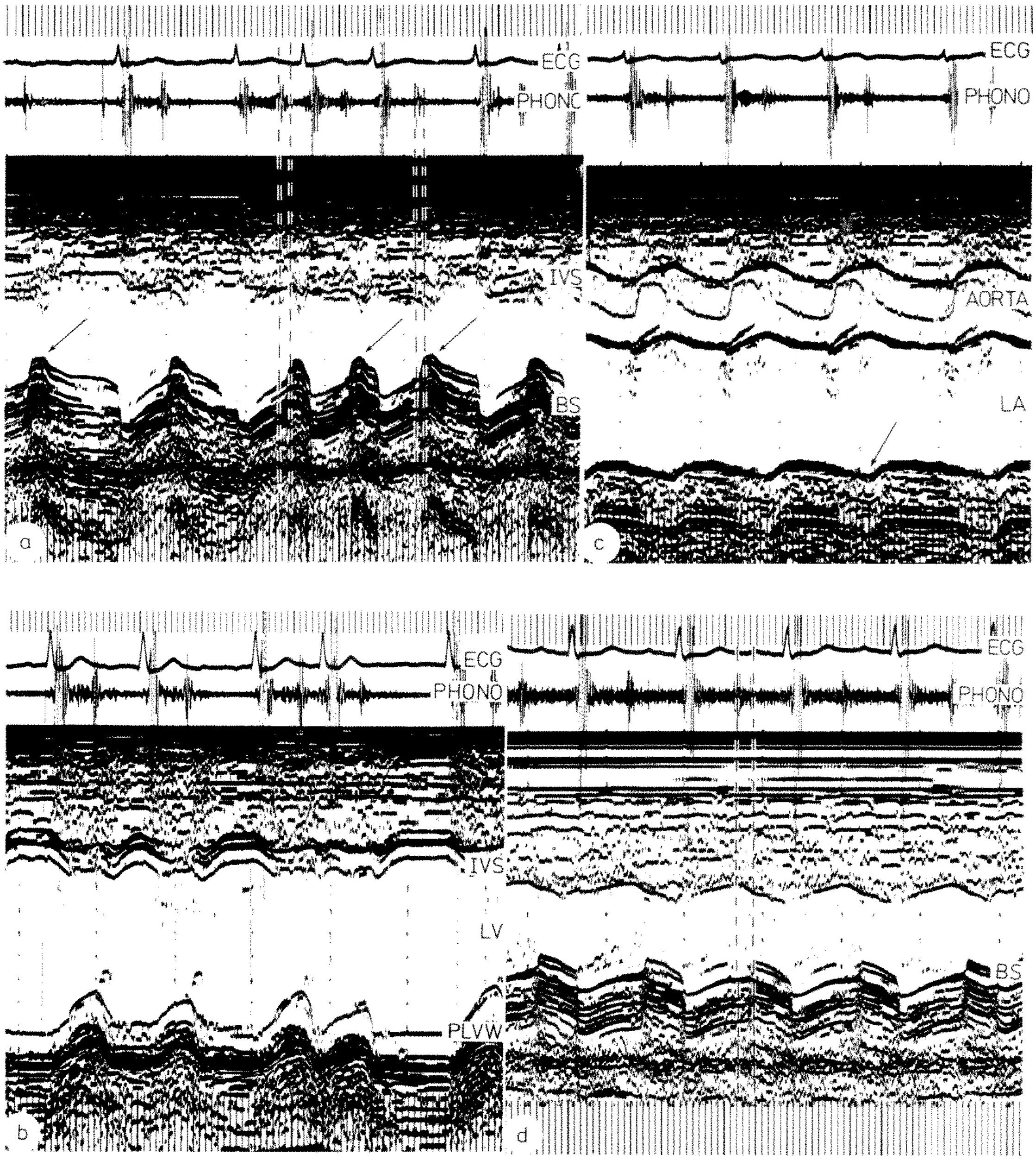

Fig. 2 *(Case 2)* (a) *Early diastolic hump of the Björk-Shiley valve echo* (arrowed). *A2-MVO interval 55 ms. Opening velocity 440 mm/s; closing velocity 890 mm/s.* (b) *Echocardiogram from body of left ventricle (LV) below Björk-Shiley valve. The cavity is dilated ($LVID_d$ = 7·0 cm). The interventricular septum (IVS) shows normal motion. The posterior left ventricular wall (PLVW) amplitude is increased at 1·75 cm (normal 0·9 to 1·4 cm). $LVID_d$, left ventricular internal diameter in diastole.* (c) *Increased diameter of left atrium at 5·2 cm (normal 1·9 to 4·0 cm) with systolic expansion* (arrowed). *The aortic leaflets approach each other during systole. These features are consistent with mitral regurgitation and reduced forward flow of a significant degree.* (d) *Postoperative echophonocardiogram. A2-MVO interval 110 ms. Loss of early diastolic hump on Björk-Shiley valve echo. LV cavity record showed return of paradoxical septal motion.*

31 mm Björk-Shiley valve in September 1978. Tricuspid stenosis (orifice 2 cm) was fully relieved by incision of the commissures and during the first two postoperative weeks there was no evidence of tricuspid regurgitation. After the third week, however, there was gradually increasing pulmonary and peripheral oedema with hepatomegaly and the jugular venous pulse showed *cv* waves 6 cm above the sternal angle. The prosthetic valve clicks were clear but a pansystolic murmur varying with respiration appeared at the lower end of the sternum together with a distinct low-pitched diastolic murmur at the apex. A soft pansystolic murmur at the apex was considered to be radiating from the tricuspid area while the apical diastolic murmur was thought to signify obstruction of the Björk-Shiley valve. Cardiac catheterisation was planned, but the patient's condition deteriorated rapidly and she died in the sixth postoperative week. An echophonocardiogram recorded 48 hours before death when the patient was critically ill is shown in Fig. 3. There is a short A2-MVO interval, normal opening and closing velocities of the Björk-Shiley valve, and early diastolic humping of the valve echo; the interventricular septum moved posteriorly in systole.

At necropsy, examination of the prosthesis showed that the sutures along 25 per cent of its circumference adjacent to the aortic valve had cut out (Fig. 4); the remaining sutures were intact and there was no thrombosis. The pyrolite disc was freely mobile. The tricuspid valve was widely patent and the cusps appeared to be functionally normal.

Discussion

Echophonocardiographic findings in prosthetic mitral valve dysfunction have previously been described. Reported non-invasive evidence of paravalvular mitral regurgitation was limited to a reduced interval between A2 and opening click (OC) and return to normal of septal motion with Starr-Edwards and Lillehei-Kaster prostheses[1 2] and the presence of a pansystolic murmur. These findings, however, are not entirely reliable; a shortened A2-OC interval may be found with an obstructed prosthetic mitral valve as well as with paravalvular regurgitation. A reduced A2-OC interval may also be found in the presence of left ventricular dysfunction.[2] Return of normal septal motion after open-heart operations may be a normal finding, partly related to the time after operation, and has been observed with clot obstruction of Lillehei-Kaster prostheses.[3] The presence, absence, and loudness of the pansystolic murmur associated with paravalvular regurgitation is unreliable as the murmur may diminish or disappear with increasing severity of regurgitation[7] and this feature is seen in the above cases. The first specific non-invasive sign associated with Björk-Shiley paravalvular regurgitation was described in two patients by Bernal-Ramirez and Phillips.[6] They noted the presence of an unusual 'hump' during the opening phase of the

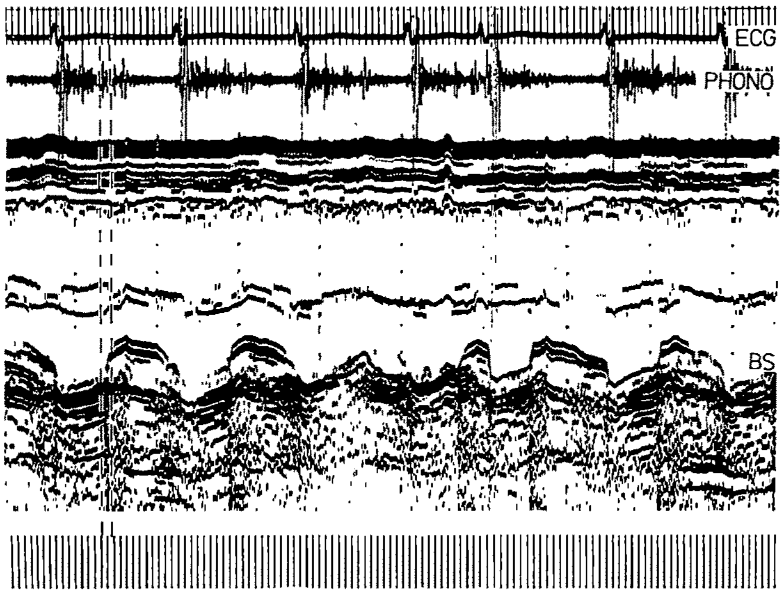

Fig. 3 *(Case 3) Echophonocardiogram showing a reduced A2-MVO interval (40 ms) and normal Björk-Shiley valve opening and closing velocities (400 and 530 mm/s, respectively). The Björk-Shiley valve echo shows an early diastolic hump.*

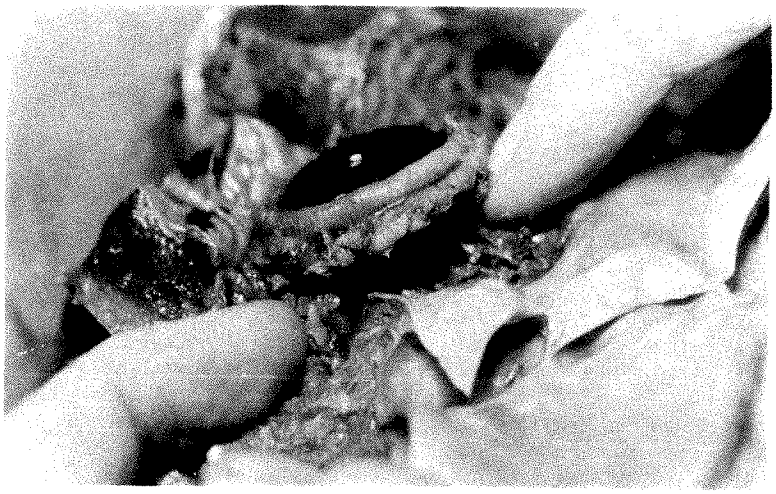

Fig. 4 *(Case 3) Björk-Shiley valve showing extensive detachment of sewing ring adjacent to aortic valve.*

valve movement together with a return of normal septal motion with this particular prosthetic valve. No phonocardiographic data were presented in this paper.

Our study confirms the echocardiographic finding of an early diastolic 'hump' and its reversibility by operation. The return to normal of septal motion is also seen. In addition, the demonstration of a reduced A2-MVO interval is in agreement with the reduced A2-OC interval found with a variety of other malfunctioning prosthetic mitral valves, compared with the normal interval of 90 ± 10 ms.[2]

Previous studies with the Starr-Edwards ball valve have shown that the echocardiographic features are the result of both ball and ring motion, and the echocardiographic findings with the Björk-Shiley valve probably represent echoes from the disc and ring also. All the patients presented had severe paravalvular regurgitation and the early diastolic hump of the Björk-Shiley valve may be associated with abnormal rocking of the partially detached mitral valve ring and disc. The sign may be confined to patients with a severe degree of regurgitation, and its prominence may depend upon the plane of abnormal rocking in relation to the ultrasound beam.

The expected echocardiographic findings of left ventricular diastolic overload seen in mitral regurgitation apply in the patient with paravalvular regurgitation (Fig. 2b). These findings, together with a reduced A2-MVO interval in the presence of good left ventricular function, normal rather than paradoxical septal motion, and an early diastolic humping of the Björk-Shiley valve appear to be useful in making a specific non-invasive diagnosis of paravalvular regurgitation associated with the Björk-Shiley prosthetic mitral valve.

In all three cases described in this paper, the echophonocardiograms were highly suggestive of this diagnosis though on admission the clinical diagnosis was obscure and the signs of severe paravalvular regurgitation unimpressive. In the first patient, the previous embolic episode, absence of a pansystolic murmur, and possible faint diastolic murmur suggested that clot was obstructing the mitral valve. In the second patient, the improvement after temporary discontinuation of digoxin therapy suggested that digitalis toxicity had played an important factor in the symptomatology, but subsequent echophonocardiography suggested the correct diagnosis. The clinical signs in the third patient, as in the first, were more suggestive of clot obstruction of the mitral prosthesis than paravalvular regurgitation.

The non-invasive investigations described may provide information with relative ease and speed, which is valuable in the diagnosis and management of surgical emergencies related to the prosthetic mitral valve. Because of individual variation, particularly in the echocardiographic appearance of the normally functioning prosthesis, their value is much enhanced by possession of good-quality postoperative reference tracings on all patients after mitral valve replacement.

We thank Dr C Foster for providing the record shown in Fig. 3.

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Br Heart J 1980; **43**: 332–343

Classification of ventricular septal defects*

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SUMMARY A classification with clinical significance is proposed for ventricular septal defect based on the study of 220 hearts with defects of the ventricular septum. All had atrioventricular and ventriculoarterial concordance with normal relations of cardiac structure. For the purpose of classification, the ventricular septum was considered as possessing muscular and membranous portions, the muscular septum itself being divided into inlet, trabecular, and outlet (or infundibular) components. Defects were observed in the area of the membranous septum, termed perimembranous defects; within the muscular septum, termed muscular defects; or in the area of septum subjacent to the arterial valves, termed subarterial infundibular defects. Perimembranous defects were found extending either into the inlet, trabecular, or infundibular septa. Muscular defects were found in or between the inlet septum, trabecular septum, or infundibular septum. Review of the angiograms showed that the classification was easy to use in the catheterisation laboratory, and our observations suggest that the precision thus obtained has considerable surgical significance.

In this report, we present a simplified concept for the classification of ventricular septal defects based on the study of over 200 pathological specimens with atrioventricular concordance, ventriculoarterial concordance, and usual relations of intracardiac structures. We have shown it to be useful for angiographic diagnosis and we believe it to have considerable surgical relevance.

Subjects and methods

The hearts studied were taken from the cardiopathological collections of the Cardiothoracic Institute, Brompton Hospital, London; the Royal Liverpool Children's Hospital; the University of Sheffield; Grimsby General Hospital; Welhelmina Gasthuis, Amsterdam; St Antonius Ziekenhuis, Utrecht: Department of Anatomy, Rijksuniversity, Leiden; the Mayo Clinic, Rochester, Minnesota; and the Children's Hospital of Pittsburgh, Pennsylvania. In all, 220 hearts were studied (Table). Only hearts with isolated or multiple ventricular septal defects in the presence of atrioventricular and ventriculoarterial concordance were included. We excluded hearts with tetralogy of Fallot[1] but included hearts with ventricular septal defect associated with valvar pulmonary stenosis. Some of the hearts have previously been illustrated[2] and an earlier concept[3] was based on study of others but the series as a whole has not been analysed previously.

The defects were studied with particular reference to their relation to the atrioventricular valves, the arterial valves, and the muscular bundles of the right ventricle, including the medial papillary muscle. The defects will be described as viewed by the angiographer or clinician, with the patient considered as being in an upright position. When the hearts have been photographed they have been oriented as far as possible to achieve this positioning. Photographs have been taken from the left ventricle, with the apex of the heart to the bottom of the frame and the aortic valve to the top.

The angiographic feasibility of the suggested classification was assessed by studying the angiograms from patients with ventricular septal defects.

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* During the course of the work Benigno Soto was a Visiting Fellow at the Cardiothoracic Institute. The work was supported by the Joseph Levy Foundation together with the British Heart Foundation, and part was carried out while R H Anderson was in receipt of the Excerpta Medica Travel Award, 1977.

Received for publication 3 September 1979

and antrioventricular and ventriculoarterial concordance and usual relations investigated in the Department of Paediatric Cardiology, University of Alabama in Birmingham, Birmingham, Alabama (courtesy of Dr L M Bargeron, Jr). Illustrative examples of the classification were obtained from these patients.

Results

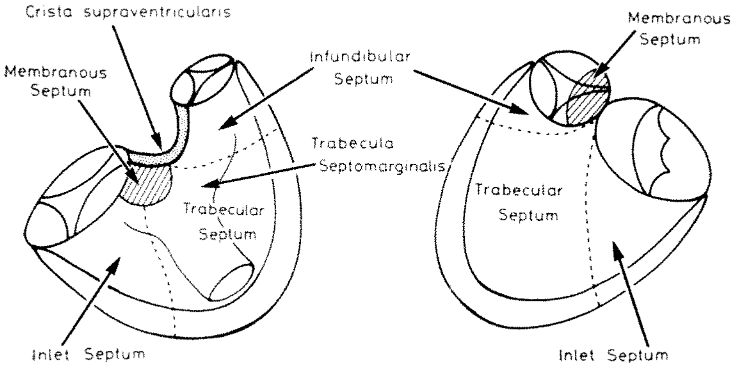
(1) CONSTITUENTS OF NORMAL VENTRICULAR SEPTUM AND TERMINOLOGY OF MUSCLE BUNDLES

For the purpose of classification of septal defects, we have considered the ventricular septum as having four components: the inlet septum, trabecular septum and outlet or infundibular septum (together making up the muscular septum), and the membranous septum (Fig. 1). The inlet septum separates the septal cusps of the mitral and tricuspid valves. It merges imperceptibly with the trabecular septum which is the largest part, extending out to the ventricular apices, and separates the finely trabeculated left ventricular apex from the more coarsely trabeculated right ventricular apical zone. It in turn merges imperceptibly with the outlet or unfundibular septum which separates the right and left ventricular outlet tracts, being considerably more extensive on its right ventricular aspect than on the left. The membranous septum in the normal heart is a small structure, divided into two parts by the insertion of the septal leaflet of the tricuspid valve. This insertion produces an atrioventricular and an interventricular component, the sizes of which vary in different hearts.

In order to describe ventricular septal defects, it is also necessary to define the nature of muscular trabeculae and bands observed in the normal right ventricle. The normal pulmonary and tricuspid valves are separated by an extensive ledge termed in *the normal heart* the crista supraventricularis. It has two components. Part of the normal crista additionally separates the aortic and pulmonary valves and is the outlet or infundibular septum. The other part of the crista between the pulmonary and tricuspid valves is the ventriculoinfundibular fold.[4] The extensive septal trabeculation of the right ventricle is also considered to be part of the crista by some authors[5] and is termed the 'septal band'. Though yet others do not consider the septal band to be part of the crista,[6] in our opinion it is better considered a separate structure and named the trabecula septomarginalis.[4] It is a septal trabecula on the right aspect of the trabecular septum, forming the superficial stratum of the septum. An important small papillary muscle of the tricuspid valve arises from the posterior limb of the trabecula septomarginalis and supports the anteroseptal commissure of the tricuspid valve. It is the medial papillary muscle. The apical part of the trabecula septomarginalis is frequently enlarged and hypertrophied, and may form a 'two-chambered right ventricle'. This feature does not affect the classification of septal defects.

(2) CATEGORISATION OF VENTRICULAR SEPTAL DEFECTS (Table)

Our study has shown that on the basis of the septal division given above, isolated defects exist for the most part in the area of the membranous septum (Fig. 2). However, as indicated by Becu *et al.*[5] and endorsed by others, these defects additionally involve the area of muscular septum surrounding the membranous septum itself, which may be present as



a) Right Ventricle b) Left Ventricle

Fig. 1 *Diagram illustrating the different muscular components of the ventricular septum and their conjunction with the membranous septum.*

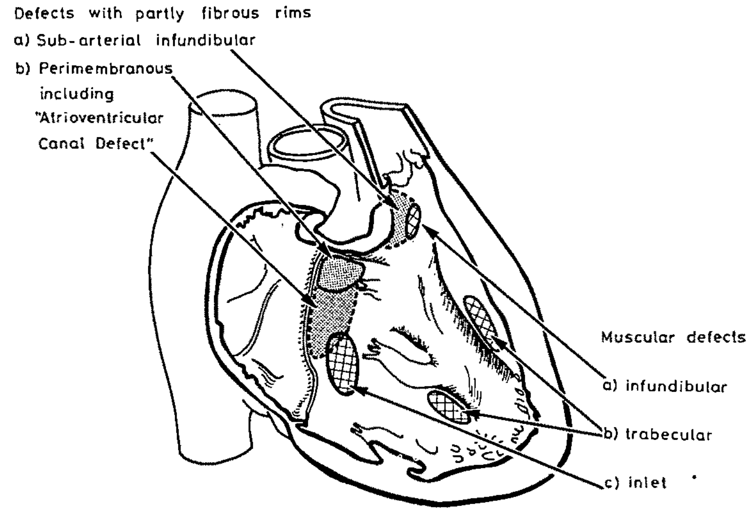

Defects with partly fibrous rims
a) Sub-arterial infundibular
b) Perimembranous including "Atrioventricular Canal Defect"
Muscular defects
a) infundibular
b) trabecular
c) inlet

Fig. 2 *Diagram illustrating the proposed classification of ventricular septal defects.*

a remnant in the roof of such defects. Many have indicated that 'membranous' is an inappropriate term for such defects. We have taken note of these objections and have employed the term *perimembranous* to describe these defects. Perimembranous defect may involve the area of either the inlet, trabecular, or infundibular septum contiguous with the area normally closed by the membranous septum (Fig. 3).

In contrast to perimembranous defects, in which part of the rim of the defect is always formed by part of the central fibrous body, other defects have purely muscular rims (Fig. 2). They are collectively termed *muscular defects*, and may exist in the area between the inlet and trabecula septa (termed inlet muscular defects), within the trabecular septum itself (termed trabecular muscular defects), or between the in-

Table *Categorisation of ventricular septal defects in 220 hearts*

Type	*Subcategories*	*No. studied*
Perimembranous	(a) Inlet	55
	(b) Trabecular	56
	(c) Infundibular	42
Muscular	(a) Posterior (inlet)	15
	(b) Trabecular	40
	(c) Infundibular	3
Subarterial infundibular		12
Mixed defects		3

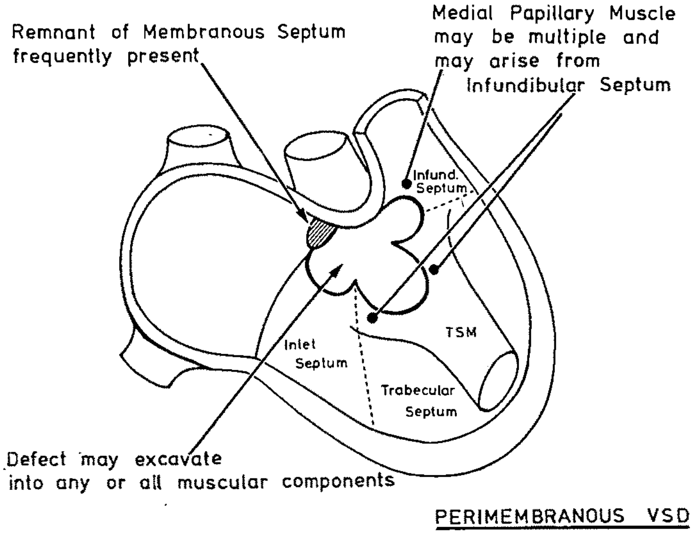

Remnant of Membranous Septum frequently present
Medial Papillary Muscle may be multiple and may arise from Infundibular Septum
Infund. Septum
TSM
Inlet Septum
Trabecular Septum
Defect may excavate into any or all muscular components
PERIMEMBRANOUS VSD

Fig. 3 *Diagram illustrating the types of perimembranous septal defect. TSM, trabecula septomarginalis; Infund, infundibular.*

fundibular and trabecular septa (termed infundibular muscular defects). A further type of defect exists in the area normally formed by the infundibular septum which does not have a purely muscular rim, and is therefore not a muscular defect, but equally is not a perimembranous defect. The non-muscular rim of these defects is formed by the contiguous arterial valves and they are termed *subarterial infundibular defects* (Fig.2).

I: Perimembranous defects

The unifying feature of these defects was that all had the area of tricuspid-mitral-aortic fibrous continuity (central fibrous body) as part of their rim (Fig. 3). The precise boundaries of the defects, and their relation to the aortic and atrioventricular valves, depended on whether the defect extended primarily into the inlet septum, the trabecular septum, or the infundibular septum.

(a) Defects extending into inlet septum When viewed from the right ventricular aspect (Fig. 4A), these defects were beneath the septal cusp of the tricuspid valve. Their atrial margin was the area of tricuspid-mitral continuity. The floor and anterior margin of the defect was the crest of the inlet and trabecular septa which ran up in the roof to merge with the infundibular septum. This septum was normally positioned and fused with the trabecular septum as in the normal heart. The medial papillary muscle was usually found above the defect. From the left ventricular aspect it was seen that the posterior margin of the defect was an extensive area of aortic-mitral-tricuspid continuity. The non-coronary cusp was in extensive continuity with the

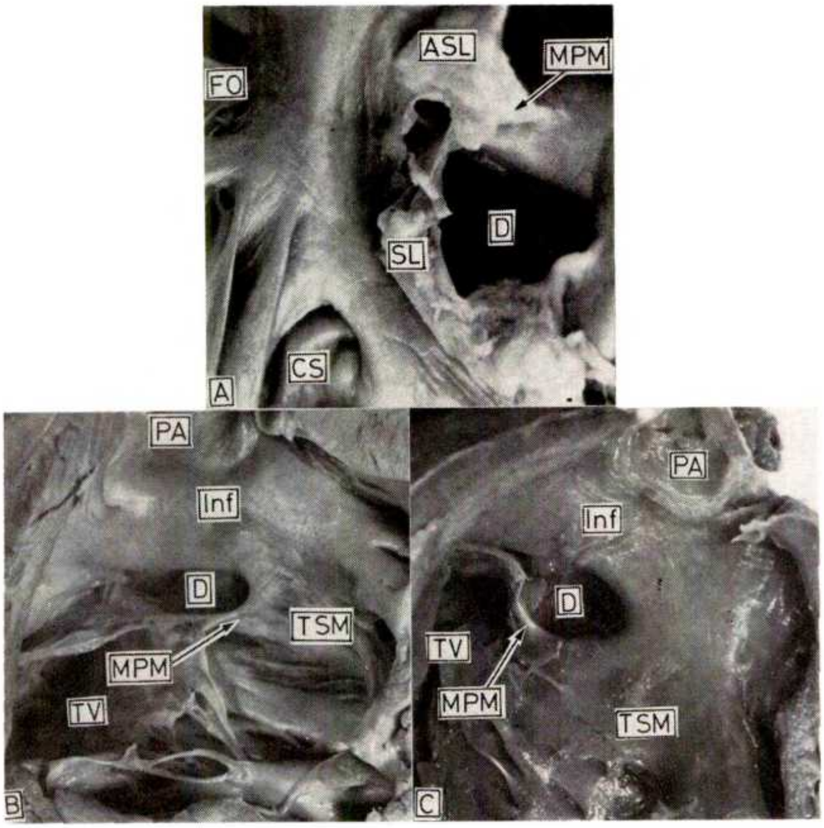


Fig. 4 *Figures of perimembranous defects extending predominantly into the inlet septum (Fig. 4A); the trabecular septum (Fig. 4B) and the infundibular septum (Fig. 4C). The inlet defect is shown in close up. It lies beneath the septal leaflet (SL) of the tricuspid valve. Medial papillary muscle (MPM) and the anterosuperior leaflet (ASL) are above the defect. FO, fossa ovalis; CS, coronary sinus. The trabecular defect (D) is behind the tricuspid valve (TV) extending between the limbs of the trabecula septomarginalis. The infundibular defect has some degree of override so that the aortic cusps are visible.*

tricuspid valve, making the aortic valve cusps the roof of much of the defect (Fig. 5A). In four hearts the septum was 'scooped' out up to the crux cordis as is usually found in atrioventricular defects (atrioventricular canal malformations or endocardial cushion defects) (Fig. 6) and in two of these hearts there was a cleft of the mitral valve. The roof of the defect in all these hearts was the infundibular septum which separated the right coronary aortic cusp from the edge of the defect. There was no malalignment of the septal structures in these hearts.

(b) Defects extending into trabecular septum In these specimens the defect was more elongated and extended towards the ventricular apex. When viewed from the right ventricle, its posterior rim was beneath the septal leaflet of the tricuspid valve, and its atrial border was a small area of aortic-mitral-tricuspid continuity (Fig. 4B). Its floor was the inlet septum, merging anteriorly with the trabecular septum buttressed by the trabecula septomarginalis. The roof of the defect was the infundibular septum, which was normally aligned relative to the trabecular septum so that no aortic overriding was present (Fig. 4B). The medial papillary muscle tended to take origin from the midpoint of the right side of the defect, and was attached to the septal commissure of the tricuspid valve across the defect. This relation was better seen from the left (Fig. 5B), this view also showing well the primary extension into the trabecular septum. The long axis of the defect was from the aortic valve towards the left ventricular apex. In many hearts

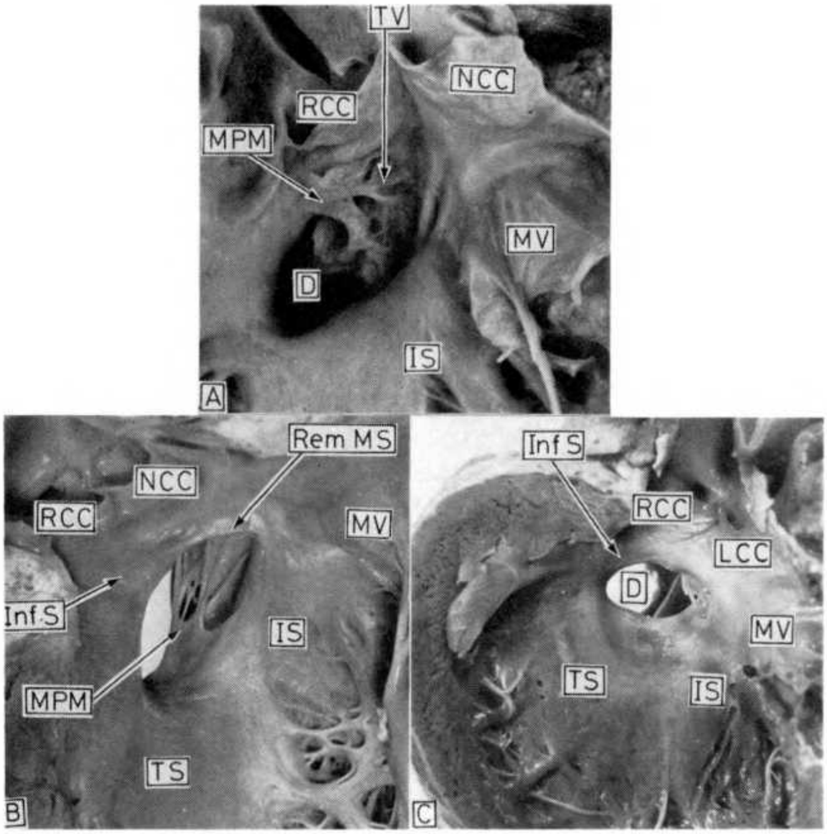


Fig. 5 *The same three defects illustrated in Fig. 4 viewed from the left ventricular aspect. Fig. 5A shows the inlet defect. The inlet septum (IS) is deficient. RCC, right coronary cusp of aortic valve; NCC, non-coronary cusp; MV, mitral valve. Fig. 5B shows the trabecular defect. The inlet septum is better formed. The defect points toward the apex and a remnant of the membranous septum (Rem MS) separates the defect from the aortic valve. Inf S, infundibular septum. Note the different orientation of the infundibular defect shown in Fig. 5C.*

remnants of tissue were delaminated from the central fibrous body in the roof of the defect, as viewed from the left. The aortic valve noncoronary cusp was in continuity with the mitral valve, but the membranous septal remnant separated the aortic valve from the tricuspid valve (Fig. 5B). The anterior margin of the roof of the defects when viewed from the left ventricle (Fig. 5B) was the infundibular septum, which formed a muscular bar separating the right coronary cusp from the defect. In these defects, therefore, a much smaller area of the aortic valve was directly contiguous with the defect as compared with the perimembranous inlet defect (compare Fig. 5A and 5B).

(c) Defects extending into the infundibulum The infundibular septum of these hearts was less well formed than in the other perimembranous defects and was usually raised to the right so that the aortic valve overrode the right ventricle (compare Fig. 4B and 4C). The atrial edge of the defect as viewed from the right ventricle was again an area of tricuspid-mitral continuity, and this became continuous anteriorly with the overriding aortic valve which formed the roof of the defect. The infundibular septum formed the anterior edge of the roof merging with the trabecular septum and trabecula septomarginalis in the anteroinferior rim of the defect. The medial papillary muscle was below the defect (Fig. 4C), but accessory papillary muscles were occasionally observed arising from the infundibular septum. The anterior extension of the defect was well seen from the left ventricular aspect (Fig. 5C). Its long axis, in contrast to the trabecular perimembranous defect, was oriented from left to right (compare Fig. 5B and 5C). The posterior margin of the defect, as viewed from the left

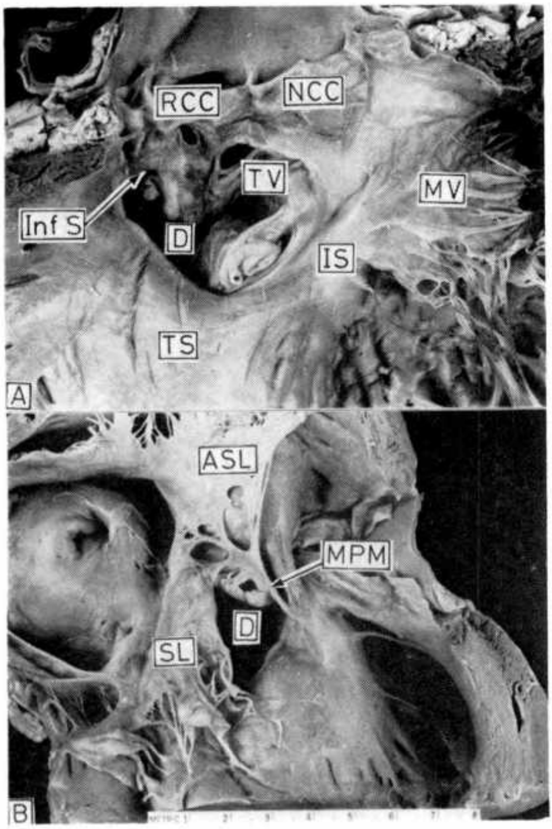


Fig. 6 *Photograph of an inlet defect (of atrioventricular canal type). The inlet septum is deficient right to the crux of the heart. Fig. 6A shows the left ventricular aspect and 6B the right ventricular aspect. There was no cleft in the mitral valve (abbreviations as before).*

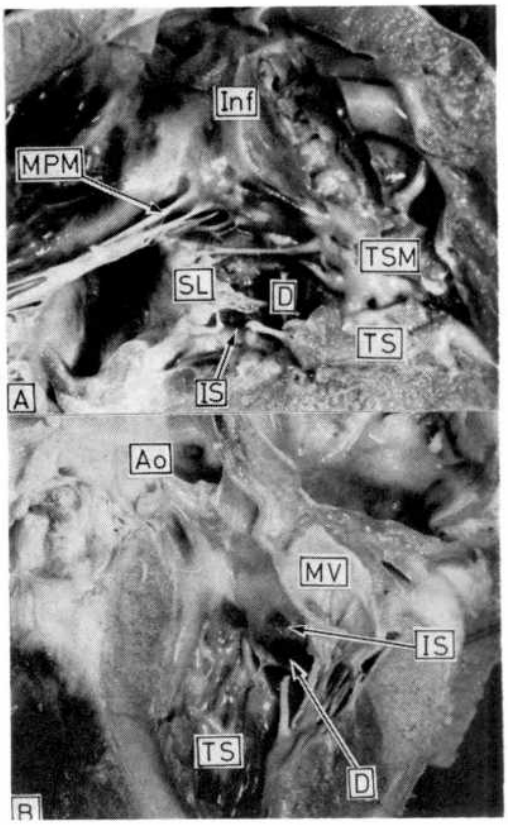


Fig. 7 *Photographs illustrating a muscular defect between the inlet septum and the trabecular septum. Fig. 7A is a right ventricular view, 7B a left ventricular view (abbreviations as before).*

ventricle, was the central fibrous body. In the posterior margin of the roof, the aortic valve noncoronary cusp was directly contiguous with the defect as a consequence of the aortic overriding, but in the anterior margin the valve was separated from the defect by the infundibular septum (Fig. 5C).

II : Muscular defects

(a) Defects in inlet area of muscular septum These defects were beneath the septal cusp of the tricuspid valve (Fig. 7A), but possessed completely muscular rims. When viewed from the left ventricle, a rim of inlet septum was present beneath and between the septal cusps of the tricuspid and mitral valves (Fig. 7B). This rim crossed obliquely the crest of the trabecular septum. It extended from the right ventricle, where it was fused with the trabecula septomarginalis posteriorly into the left ventricle, where it fused with the trabecular septum. Frequently this latter fusion point was overlaid by a prominent posterior trabecula. The size of the defect varied according to the degree of development of the trabecular septum. A membranous septum was present and intact in these hearts, having both atrioventricular and interventricular components.

(b) Defects in the trabecular area of the muscular septum These defects in the muscular septum were frequently multiple and better appreciated from the left than the right side. The openings as seen from the right ventricle were closely related to the edges of the trabecula septomarginalis (Fig. 8A). From the left it was seen that the defects were within the trabecular septum (Fig. 8B) but their position was variable. The membranous septum was normally formed in these hearts.

(c) Defects in infundibular area of septum Three specimens were encountered in which a defect with entirely muscular rims was located between the ventricular outflow tracts. As viewed from the right ventricle, the roof of the defect was the remnant of the infundibular septum. This merged anteriorly with the anterior limb of the trabecula septomarginalis (Fig. 9A) which formed the floor of the defect. Posterior, the infundibular septum merged with the ventriculoinfundibular fold and the posterior limb of the trabecula septomarginalis. This fusion of muscular structures formed a muscular rim in front of a normally formed and positioned membranous septum. When viewed from the left ventricle, the defect was seen to be completely separated from the aortic valve by the infundibular septum. Posterior to this the aortic valve was continuous with the central fibrous body (Fig. 9B). The difference between this defect and the perimembranous infundibular defect was that the aortic valve did not form part of the rim of the defect (compare Fig. 5C and 9B).

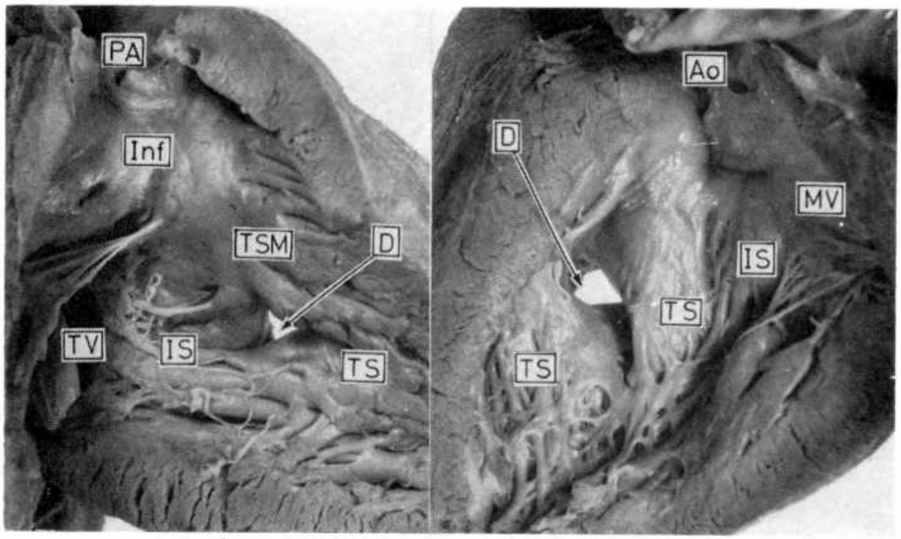


Fig. 8 *A trabecular septal defect viewed from the right ventricle* (A), *and the left ventricle* (B).

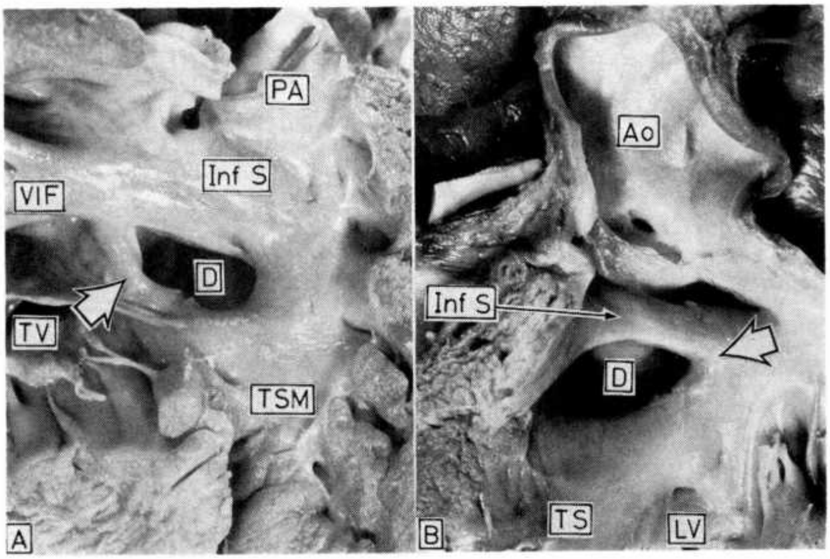


Fig. 9 *A muscular defect of the infundibular septum viewed from the right ventricle* (A), *and the left ventricle* (B). *Note that the posterior limb of the trabecula septomarginalis* (arrowed) *fuses with the ventriculoinfundibular fold (VIF) in the posterior rim of the defect. The infundibular septum separates the defect from the pulmonary valve. The membranous septum is intact (abbreviations as before).*

III: Subarterial infundibular defects

These defects were similar to the muscular infundibular defects except that the infundibular septum was totally deficient, so that the aortic and pulmonary valves were contiguous in the roof of the defect (compare Fig. 9 and 10). Because of this, the left coronary and right coronary aortic valve cusps were free to move into the right ventricular outflow tract, and some of the hearts had aortic cusp prolapse. In the floor of the defect, as in the muscular infundibular defects, the posterior limb of the trabecula septomarginalis extended to the ventriculoinfundibular fold, forming a muscular rim in front of a normally formed membranous septum

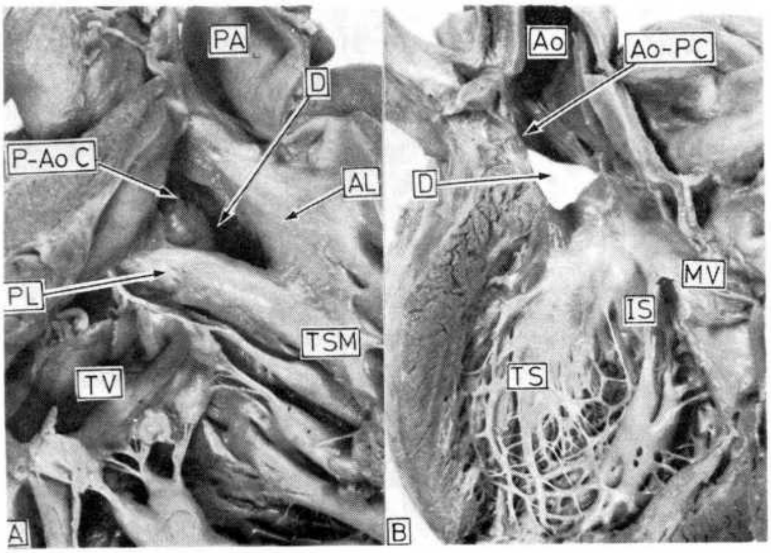


Fig. 10 *Right ventricular* (A) *and left ventricular* (B) *views to a subarterial septal defect. The posterior limb (PL) of the trabecula septomarginalis fuses with the ventriculoinfundibular fold separating the defect from the normally formed membranous septum. Deficiency of the infundibular septum permits pulmonary to aortic fibrous continuity, P-AoC, Ao-PC.*

(Fig. 10). When viewed from the left ventricle, the right and left coronary cusps of the aortic valve formed the entire roof of the defect, being contiguous with the pulmonary valve and distinguishing the defects from muscular infundibular defects (compare Fig. 9B and 10B).

ANGIOGRAPHIC CORRELATIONS

Examination of angiograms from patients studied at the University of Alabama in Birmingham (courtesy of Dr L M Bargeron Jr) showed that using projections designed to profile the ventricular septum[7] it was possible to distinguish perimembranous (Fig. 11) from muscular (Fig. 12) and subarterial infundibular (Fig. 13) defects.[8] Furthermore, careful assessment of each type showed that it was possible to distinguish the three varieties of both perimembranous (Fig. 11A-C) and muscular (Fig. 12A-C) defects.

Discussion

The classification of isolated ventricular septal defect here presented is an eclectic modification of categorisations of earlier workers[5 9-14] together with our own earlier attempts to achieve a satisfactory nosology.[2 3] In the present categorisation we have used purely descriptive terms to describe the three components of the muscular septum delineated on developmental grounds by Goor *et al.*,[14] and we believe that this usage has increased the value of the categorisation. Certainly by using angiographic views designed to profile the ventricular septum[7] it has proved feasible to distinguish defects existing in relation to these three parts of the muscular septum in addition to distinguishing between perimembranous, muscular, and subarterial defects.

Although it clearly has value in angiographic diagnosis, it is our contention that it has con-

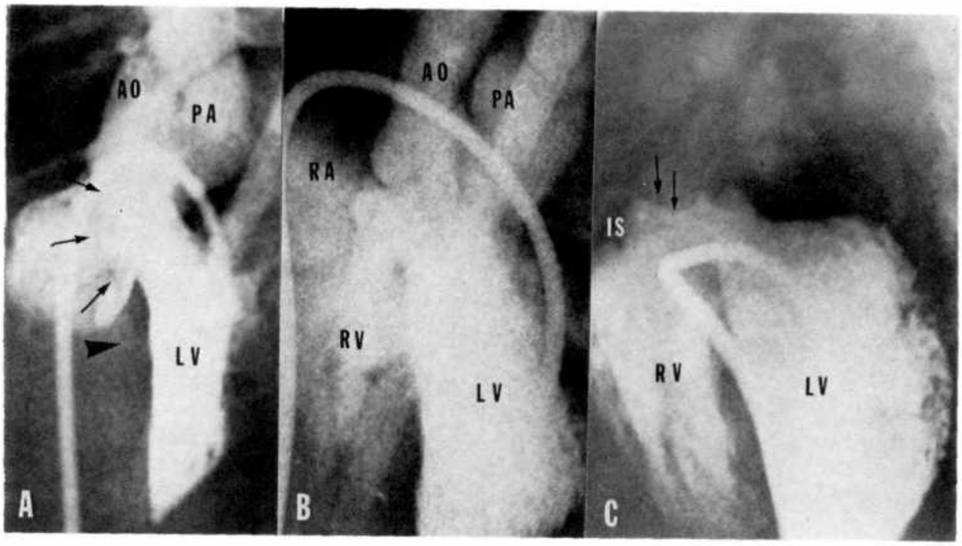


Fig. 11 *Angiographic feature of perimembranous ventricular septal defects seen in 'four chamber' views. The diagnoses were subsequently verified at operation.* (A) *Perimembranous ventricular septal defect excavated in the inlet septum. The ventricular septal defect is large, roofed by the aortic valve. The inferior border is near the crux of the heart* (arrow-head). *A large segment of the septal tricuspid leaflet* (arrow) *is in contact with the defect, but both atrioventricular valves are well formed. AO, aorta; PA, pulmonary artery; LV, left ventricle.* (B) *Perimembranous defect excavated in the trabecular septum. The defect is roofed by the aortic valve (non-coronary cusp) and its anterior border is the upper portion of the trabecular septum* (arrow). *Notice that the contrast media from the left ventricle (LV) opacifies the right ventricle (RV) and also the right atrium (RA). The left ventricle—right atrium connection is through the medial commissure of the tricuspid valve which covers the ventricular septal defect. AO, aorta; PA, pulmonary artery.* (C) *Perimembranous defect excavated in the infundibular septum. The defect is located immediately beneath the right and non-coronary (aortic) cusps* (arrows). *The contrast media injected into the left ventricle (LV) passes into the right ventricle (RV) opacifying the trabeculated portion mainly. The infundibular septum (IS) is deviated anteriorly, leaving the right and non-coronary cusps above the right ventricle.*

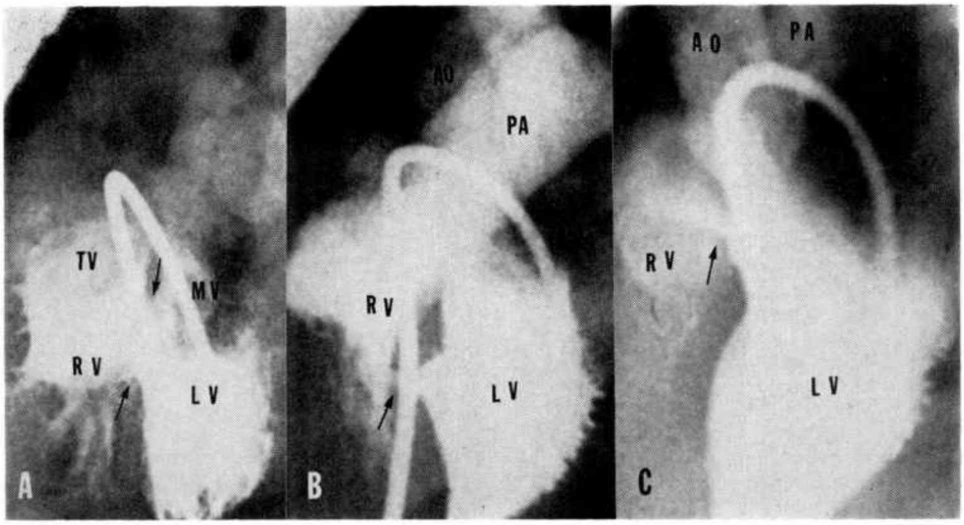


Fig. 12 *Angiographic feature of muscular ventricular septal defects seen in 'four chamber' views. The diagnosis in each case was verified at surgery.* (A) *Muscular inlet. The defect* (arrows) *is located in the inlet portion of the ventricular septum discontinuous from the mitral and tricuspid annuli. RV, right ventricle; LV, left ventricle.* (B) *Muscular trabecular. The defect* (arrow) *is located in the trabecular portion of the septum near its posterior border. RV, right ventricle; LV, left ventricle; AO, aorta; PA, pulmonary artery.* (C) *Muscular infundibular. The defect* (arrow) *is in the right border of the left ventricular outflow tract, separated from the arterial and atrioventricular valves. Note the early opacification of pulmonary artery (PA). AO, aorta; RV, right ventricle; LV, left ventricle.*

siderable value in surgical viewpoint. The main thrust of the surgical classification of Kirklin and his colleagues[11 12] was to distinguish those defects in relation to the aortic valve ('high' defects) from those not in relation to the aortic valve ('low' defects). Our classification refines this possibility, since it distinguishes defects with entirely muscular rims, which clearly are never directly related to the aortic valve, from those with rims formed by intrinsically fibrous tissue in which the aortic valve forms part of this rim. It further distinguishes the latter group into those in which the aortic valve is related to the defect as part of the central fibrous body (perimembranous defects) from those in which it is related to the defect in continuity with the aortic and pulmonary valves (subarterial infundibular defects). However, the surgical value of the present classification goes far beyond the relation of the defect to the aortic valve. The recognition of a defect as perimembranous, muscular, or infundibular immediately alerts the surgeon to the likely disposition of the conduction tissues. If a defect is perimembranous, previous studies[15–17] have shown that the atrioventricular conduction axis will always be related to the posteroinferior quadrant of the defect (to the surgeon's right hand as viewed from either the right atrium (Fig. 14) or a right ventricular infundibulotomy). In contrast, a muscular defect in the inlet septum will have the conduction tissue related to its superoanterior quadrant (to the surgeon's left hand as viewed from atrium (Fig. 14) or infundibulum). Muscular defects in the trabecular septum are unlikely to be related to the non-branching or branching components of the conduction tissue axis, though they may be related to bundle-branches,[17] while infundibular, muscular, or subarterial defects are unrelated to the conduction tissue.[18] The recognition of a perimembranous defect as inlet, trabecular, or infundibular also provides information regarding the direct relation of the ventricular conduction tissue axis to the septal rim.[18]

In addition to providing this information which we believe to be of value to both diagnostician and surgeon, our study helped to clarify several points which previously had given us some problems. Firstly, it became evident that though most defects were in the region of the membranous septum, they represented more than mere absence of the membranous septum. Becu *et al.*[5] have previously emphasised this point. Goor and his colleagues[14 19] similarly recognised that most defects in this area

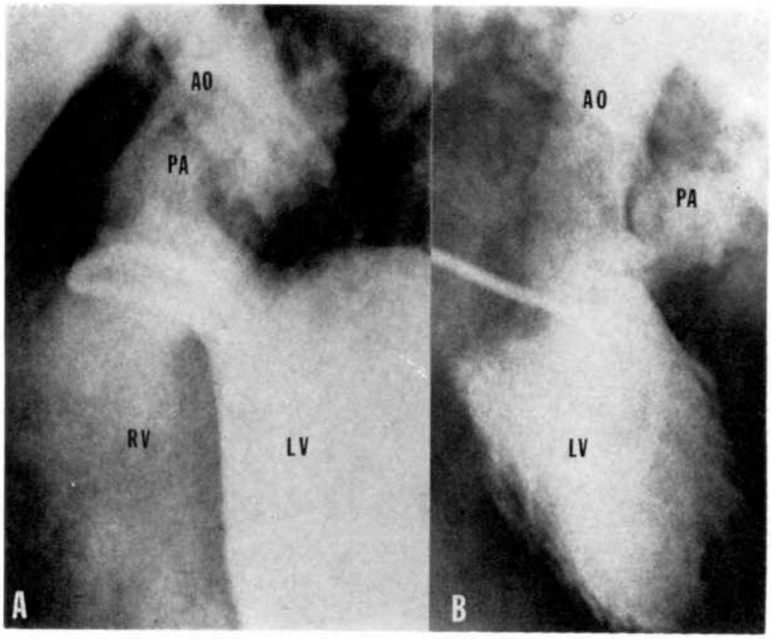


Fig. 13 *Angiographic appearance of subarterial ventricular septal defect, left ventriculogram in* (A) *'long axial', and* (B) *elongated right anterior oblique views. The defect is located in the infundibular septum roofed by the arterial valves seen in both projections. The atrioventricular valves are not related with the ventricular septal defect. AO, aorta; PA, pulmonary artery; RV, right ventricle; LV, left ventricle.*

were not 'true' defects of the membranous septum, but they did recognise a small group which they categorised as membranous defects. In our series, we did not encounter any defects so small that we considered them truly to be mere absence of the interventricular membranous septum. Instead, it was our interpretation that all defects resulted from deficiency of the muscular septum in the environs of the interventricular membranous septum, which was frequently present as part of the border of the defects. Hence, our suggestion of the term 'perimembranous' to describe these defects, and our subdivision of the group depending on whether the muscular deficiency affected primarily the inlet, trabecular, or outlet components of the muscular septum. It is possible that tiny defects could result simply from absence of the interventricular membranous septum, or that alternatively a small perforation could be found in an aneurysmal membranous septum which has closed an existing defect. If required, the term 'membranous septal defect' could accurately be applied to such lesions.

The second point relates to the so-called 'isolated ventricular septal defect of persistent common atrioventricular type'.[20] As one of us has indicated, most of these defects are really defects of the inlet septum extending into the area of the membranous septum, and have presently been categorised as perimembranous inlet defects.[2] It was significant that not all the perimembranous inlet defects we

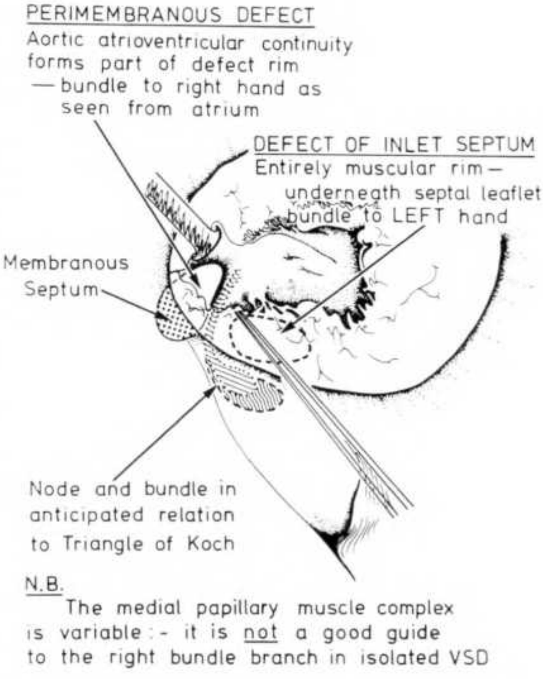

PERIMEMBRANOUS DEFECT
Aortic atrioventricular continuity forms part of defect rim — bundle to right hand as seen from atrium
DEFECT OF INLET SEPTUM
Entirely muscular rim — underneath septal leaflet bundle to LEFT hand
Membranous Septum
Node and bundle in anticipated relation to Triangle of Koch
N.B.
The medial papillary muscle complex is variable :- it is not a good guide to the right bundle branch in isolated VSD

Fig. 14 *Diagrammatic representation of the different relations of perimembranous and muscular inlet defects to the atrioventricular conduction tissue axis as viewed by the surgeon from the right atrium.*

studied exhibited the stigmata of atrioventricular defects, namely disproportion between the inlet and outlet dimensions of the muscular septum and malorientation of the aortic valve. Indeed, not all the defects illustrated by Neufeld *et al.*[20] showed these features. Only four of the 55 inlet perimembranous defects we examined exhibited the 'scooped-out' septum so typical of the atrioventricular defect, two of these having clefts in their mitral valves. If the term 'isolated atrioventricular canal defect' is to be used, it is our preference to restrict it to these hearts, while still preferring the description 'perimembranous inlet defect with gross deficiency of the inlet septum' as being less ambiguous.

Thus, we have presented an eclectic classification of ventricular septal defects based on the premise that the ventricular septum has membranous and muscular portions, the latter itself having inlet, trabecular, and outlet components. We have shown that the classification, based on study of pathological material, is of value in the angiographic laboratory, and that the diagnostic precision thus afforded has considerable surgical significance. We offer the classification as a simple alternative to those presently available.

We are indebted to our colleagues who permitted us to study hearts from their collections, namely, Professor F J Macartney, The Hospital for Sick Children, London, UK; Dr J L Wilkinson, Royal Liverpool Children's Hospital, UK; Dr L M Gerlis, Grimsby General Hospital, UK; Professor J Emery, Sheffield University, UK; Dr A Oppenheimer-Decker, Leiden, The Netherlands; Dr J Van Gorp, Utrecht, The Netherlands, and Dr J R Zuberbuhler, Pittsburgh, Pa, USA. We thank Dr J W Kirklin, Birmingham, Alabama, USA, for his advice and critical appraisal of the manuscript, and Dr L M Bargeron Jr, Birmingham, Alabama, USA, for permission to study and publish the angiograms of his patients.

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Br Heart J 1980; **43:** 344–350

Cardiac performance in hypertension re-evaluated through a combined haemodynamic ultrasonic method

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SUMMARY From echocardiographic measurements, 39 patients with established, uncomplicated primary hypertension (diastolic pressure >100 mmHg) were classified as follows: normal-sized heart (group 1, 10 cases); concentric left ventricular hypertrophy (group 2, 18 cases); left ventricular hypertrophy and cavity enlargement (group 3, 11 cases). Eighteen age-matched healthy subjects were investigated as a control group.

Systolic and diastolic arterial pressure increased progressively from group 1 to 2 to 3. Left ventricular function, assessed from the relation between diastolic diameter and stroke index, was maintained in group 1, increased in group 2 (in spite of the greater pressure load), and reduced in group 3, in comparison with controls. Similarly, the mean velocity of circumferential fibre shortening (VCF) was normal in group 1, significantly increased in group 2, and reduced in group 3. It was impossible to discern whether the different behaviour of VCF in group 2 and in group 3 reflected opposite changes in ventricular contractility, or in wall stress during ejection, or in both.

At variance with previous conclusions (which were based on utilisation of electrocardiographic and chest *x*-ray criteria to define hypertrophy) it is suggested that left ventricular concentric hypertrophy in man consequent to sustained hypertension is associated with an improved function. Whether this feature depends upon an augmented contractility or a ventricular unloading effect related to hypertrophy remains uncertain.

Afterload is a major determinant of left ventricular function in systemic hypertension. At comparable levels of arterial pressure and vascular resistance, afterload may be reduced when ventricular hypertrophy develops, or increased when the cavity becomes enlarged. Evaluation of cardiac performance in hypertension requires a precise assessment of the circulatory load as well as the ventricular dimensions and wall thickness.

In earlier clinical studies, including our own,[1–3] it was reported that the performance of the hypertrophied heart was impaired in hypertensive patients. There are, however, reasons for reconsidering the validity of this conclusion: thus, conventional electrocardiographic criteria for hypertrophy have obvious limitations arising from the occurrence of false-positive[4] and false-negative[5] diagnoses; in addition, chest *x*-ray criteria of left ventricular enlargement to diagnose hypertrophy[2] evidently precludes a separate analysis of concentric hypertrophy and, respectively, dilatation of the left ventricle.

Echocardiography provides an accurate method for the estimation of left ventricular wall thickness and dimensions; the ultrasound method identifies concentric hypertrophy more often than electrocardiograms or chest *x*-rays[6]; echocardiography also makes it possible to integrate haemodynamic findings and measurements of wall stress.[7] A combination of the two methods was used in a large hypertensive population in this study.

Subjects and methods

Thirty-nine men in hospital with primary systemic arterial hypertension were the subjects of this investigation. All had repeated sphygmomanometric blood pressure readings of 180/100 mmHg or more. Patients were selected who were less than 60 years of age, and had no history or signs of heart failure, pulmonary disease, valve lesions, coronary heart disease, or idiopathic myocardial disease. All had normal serum electrolyte concentrations; all were

Received for publication 5 March 1979

in regular sinus rhythm without conduction abnormalities; none had received digitalis at any time or antihypertensive treatment for at least one month. In all it was possible to record a technically satisfactory left ventricular echocardiogram; subjects were excluded who had a ratio of septal to posterior wall thickness greater than 1·3, or abnormal interventricular septal motion. Patients were not included if they were in urgent need of treatment.

A control group of 18 subjects included healthy volunteers and patients who had no signs of cardiovascular disease and who were taking no drugs with any action on the cardiovascular system. All subjects gave free consent to the investigation in the full knowledge of the procedures to be undertaken. Hypertensives were divided into three groups according to the following echocardiographic criteria: group 1 (10 cases) consisted of subjects in whom septal and posterior wall thickness and end-diastolic left ventricular minor axis were within one standard deviation of the normal control measurement; group 2 (18 cases) consisted of subjects with normal or reduced left ventricular minor axis and both septal and posterior wall thickness exceeding mean plus one standard deviation of control measurement; in group 3 (11 cases), wall thickness was within the same range as in group 2 but end-diastolic minor axis exceeded the mean plus one standard deviation for this group. These criteria defined the structural characteristics of the heart: normal heart (group 1), concentric hypertrophy (group 2), hypertrophy associated with left ventricular cavity enlargement (group 3). Examples of echocardiograms in each hypertensive group are illustrated in Fig. 1.

HAEMODYNAMIC METHODS

One week after admission, after the diagnosis of essential hypertension had been established, and after the patients had been familiarised with the laboratory and with the investigators, circulatory measurements were performed in the fasting state, in the supine position, without premedication. A no. 7 flow-directed Swan-Ganz catheter was inserted into an antecubital vein and advanced to the pulmonary artery and to the wedge position. A no. 6 radiopaque polyethylene catheter, introduced percutaneously into a brachial artery, was advanced to the root of the aorta, and was used to monitor arterial pressure and to withdraw blood for dye dilution cardiac output measurements. Reproducible dye dilution curves were obtained using a Gilford densitometer after rapid injection of indocyanine green dye (5 mg) into the main pulmonary artery. The area under each dye dilution curve was measured by planimetry and cardiac output calculated by the standard Hamilton method. Pressures were measured using Statham P23de and P23db strain gauge transducers (zero reference level 5 cm below sternal angle). Mean pressures

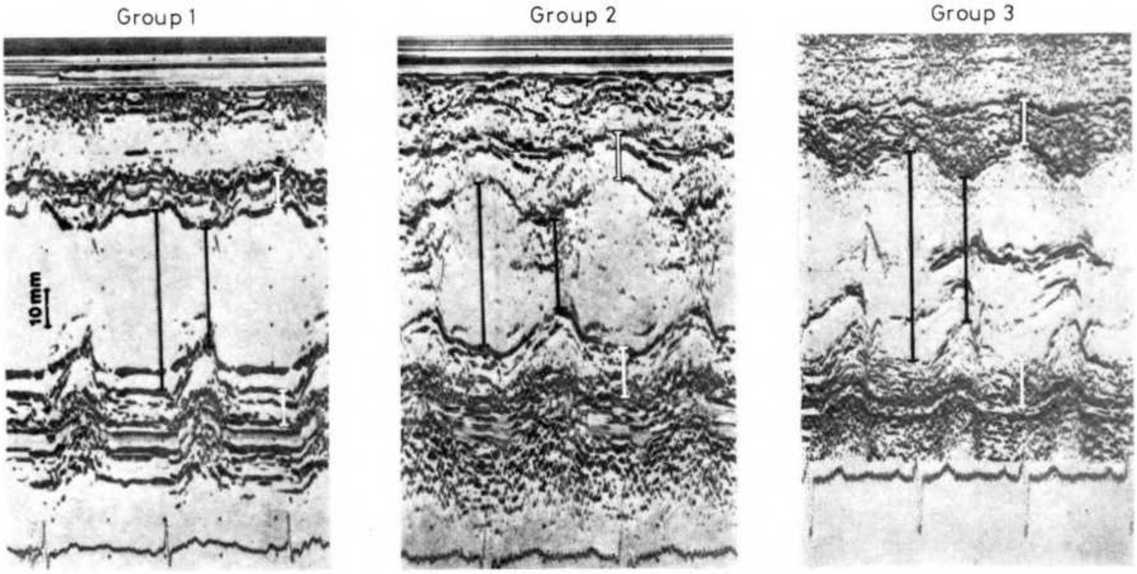

Fig. 1 *Examples of left ventricular echocardiogram in the three hypertensive groups. Wall thickness and systolic and diastolic diameters are indicated by white and black lines, respectively.*

were obtained by electronic damping. Left ventricular ejection time was measured from the aortic pressure pulse recorded at a paper speed of 100mm/s; measurements were made to the nearest 5 ms from the beginning of the upstroke to the trough of the incisura on five consecutive beats and an average value calculated. Mean systolic ejection rate (MSER) was determined by dividing the stroke index by the left ventricular ejection time. Systemic vascular resistance (–5) was calculated using the formula:

$$\mathrm{SVR\ (dynes\ s\ cm^{-5})} = \frac{\overline{\mathrm{AP}} - \overline{\mathrm{RAP}} \times 1{\cdot}332 \times 60}{\mathrm{CO}}$$

where $\overline{\mathrm{AP}}$ is arterial mean pressure (mmHg), $\overline{\mathrm{RAP}}$ is right atrial mean pressure (mmHg), and CO is cardiac output (l/min).

ECHOCARDIOGRAPHIC METHODS

An Echo-Cardio-Visor ultrasound unit (Organon Teknika) was used. Ultrasound measurements of the left ventricle were made as described by Feigenbaum *et al.*[8] Patients were lying, turned slightly to the left, with 20° elevation of the head; the transducer was placed in the third or fourth intercostal space to the left of the sternum and was directed posteriorly and medially until the characteristic pattern of mitral valve motion was observed. The ultrasonic beam was then directed laterally and slightly inferiorly to locate a plane in which the interventricular septum and the endocardium and epicardium of the left ventricular posterior wall could be observed simultaneously. The gain, damping, and reject controls were adjusted to display echoes from these structures optimally, to show their characteristic patterns of motion. These were displayed in a time-motion mode and recorded using a Honeywell strip chart recorder at a paper speed of 50 mm/s. The tip of the mitral valve was chosen as the best reproducible reference point along the left ventricular long axis for comparing quantitative measurements in different hearts. The left ventricular internal dimensions were measured at end-diastole at the time of the R wave of the electrocardiogram, and at end-systole at a time when the distance between the posterior wall and septum was least; the measurements were made from the endocardium of the posterior wall to the left side of the septum. The thickness of the left ventricular posterior wall was measured between endocardial and epicardial echoes and the thickness of the septum between the right and left ventricular endocardial echoes at end-diastole. From these measurements left ventricular circumferential wall stress (CWS) and mean velocity of circumferential shortening (V_{CF}) were calculated. Circumferential wall stress (dynes/cm^2) at the time of aortic valve opening was taken as an index of left ventricular preejection afterload, and was calculated using the formula of Sandler and Dodge,[9] modified by Ratshin *et al.*[10]:

$$\mathrm{CWS} = \frac{\mathrm{PD}/2}{\mathrm{h}}\left(1 - \frac{\mathrm{D}}{8\,(\mathrm{D}+\mathrm{h})}\right) \times 1334$$

where P is the aortic diastolic pressure (mmHg), D is the left ventricular internal minor dimension (cm), and h is the left ventricular posterior wall thickness (cm). The normalised mean velocity of circumferential fibre shortening (circ/s) was calculated using the equation of Fortuin *et al.*[11]:

$$V_{CF} = \frac{D_D - S_D}{\mathrm{LVET} \times D_D},$$

where D_D is the end-diastolic diameter (cm), S_D is the end-systolic diameter (cm), and LVET is the left ventricular ejection time (s). All the haemodynamic and echocardiographic measurements were made in the steady state, when patients were comfortable and heart rate and pressures stable; in all cases measurements were begun at least 30 minutes after completing the catheterisation procedure. Measurements were made twice, at 15-minute intervals, and the average of the two measurements calculated. Statistical significance of the differences between the groups was evaluated by analysis of variance.

Results

Age and body surface area were comparable in the three hypertensive groups and not significantly different in the control group. The echocardiographic measurements are reported in the Table. The averages of the haemodynamic measurements are presented graphically in Fig. 2. Heart rate was similar in the hypertensive and control groups. Arterial pressure (systolic and diastolic) and total peripheral resistance were significantly increased in all three hypertensive groups ($p < 0{\cdot}01$). Cardiac index was normal in group 1, increased in group 2 ($p < 0{\cdot}05$), and reduced in group 3 ($p < 0{\cdot}01$), in comparison with the control group. The mean velocity of circumferential fibre shortening was normal in group 1, but was increased in group 2 ($p < 0{\cdot}01$), and reduced in group 3 ($p < 0{\cdot}01$). The changes in mean systolic ejection rate were similar;

the differences were related to larger stroke index and shorter ejection time in group 2 and to smaller stroke index and longer ejection time in group 3, in comparison with the control group. Pre-ejection left ventricular circumferential wall stress was increased in groups 1 and 3 ($p < 0{\cdot}01$), and slightly reduced in group 2 compared with the control group. Because of the nature of the formula for wall stress, the raised aortic diastolic pressure in group 1 accounted for the increased circumferential wall stress in this group. In group 2, in spite of the raised aortic diastolic pressure, circumferential wall stress was unchanged or even reduced; this was related to the increased wall thickness associated

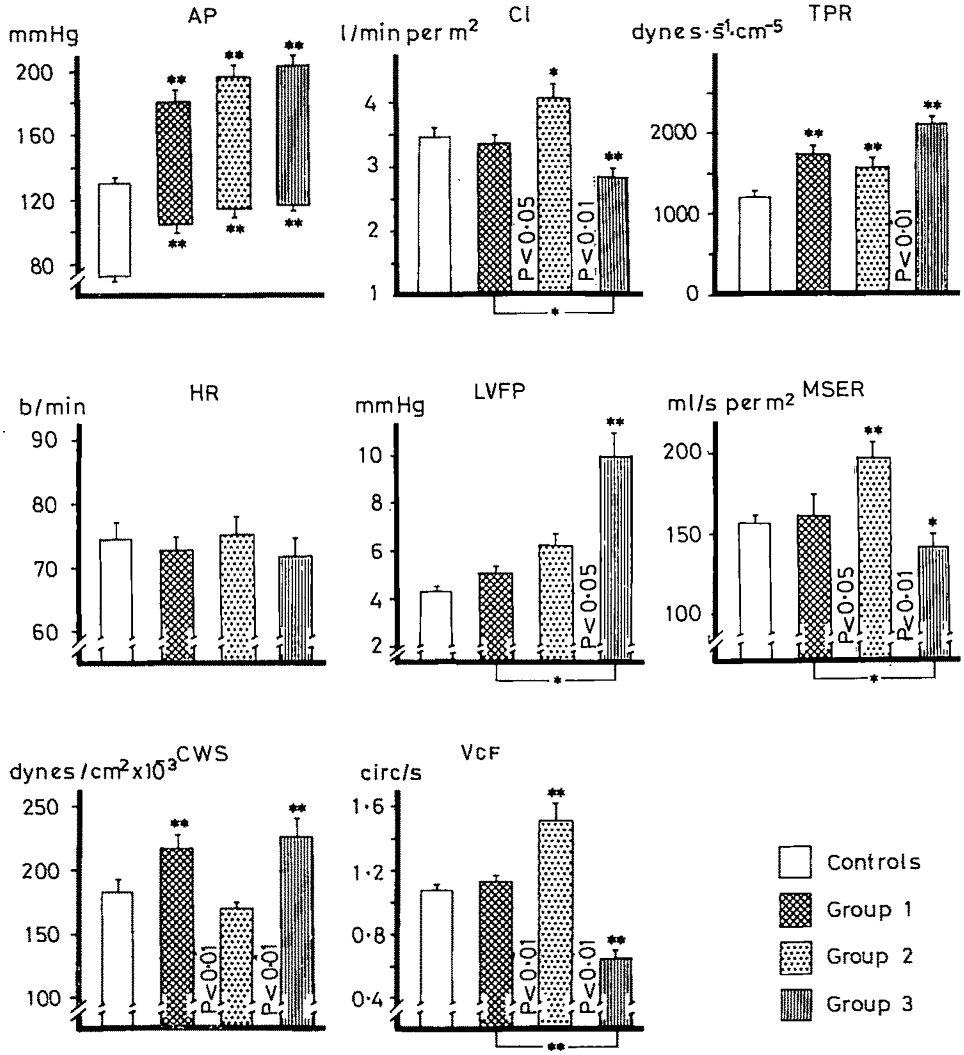

Fig. 2 *Haemodynamic measurements in 18 normal control subjects and in three groups of patients with essential hypertension. Group 1, 10 patients with normal-sized heart; group 2, 18 patients with concentric left ventricular hypertrophy; group 3, 11 patients with hypertrophy and left ventricular cavity enlargement. Bars represent the mean and SEM for the group. * and ** indicate p values of* $< 0{\cdot}05$ *and* $< 0{\cdot}01$*, respectively, for differences between hypertensive groups and controls; p values for differences between the hypertensive groups are also shown in the figure. AP, arterial pressure (systolic and diastolic); CI, cardiac index; TPR, total peripheral vascular resistance; HR, heart rate, LVFP, left ventricular filling pressure; MSER, mean rate of systolic ejection; CWS, circumferential wall stress;* V_{CF}*, mean rate of circumferential fibre shortening.*

Table *Echocardiographic values (averages and SD)*

Groups	*LV posterior wall thickness (mm)*	*LV septal wall thickness (mm)*	*LV internal dimensions (mm)* D_D	S_D
Control subjects	9·3 (1·5)	9·6 (1·2)	47·7 (1·5)	32 3 (2·5)
Hypertensive:				
Group 1	9·9 (1)	9·7 (1·3)	46·6 (3·1)	31·2 (4·6)
Group 2	13·7* (1·5)	13·7* (1·1)	44·1* (3·8)	26·7* (5·3)
Group 3	13·1* (1·6)	13·5* (1·4)	55·3*† (6)	44·6*† (8·3)

*Significant differences from control subjects ($p < 0·01$).
†Significant differences from hypertensive group 2 ($p < 0·01$).

with normal or reduced ventricular minor axis. In group 3, in which both aortic diastolic pressure and left ventricular dimensions were increased, circumferential wall stress was increased. Left ventricular filling pressure (pulmonary artery wedge mean pressure) was increased in all three hypertensive groups, though the difference from normal was statistically significant only in group 3 ($p < 0·01$).

Fig. 3 illustrates the relation between stroke index and left ventricular diastolic diameter. Stroke index was increased in group 2 compared with normal and reduced in group 3, even though diastolic dimension was smaller in the former and greater in the latter group.

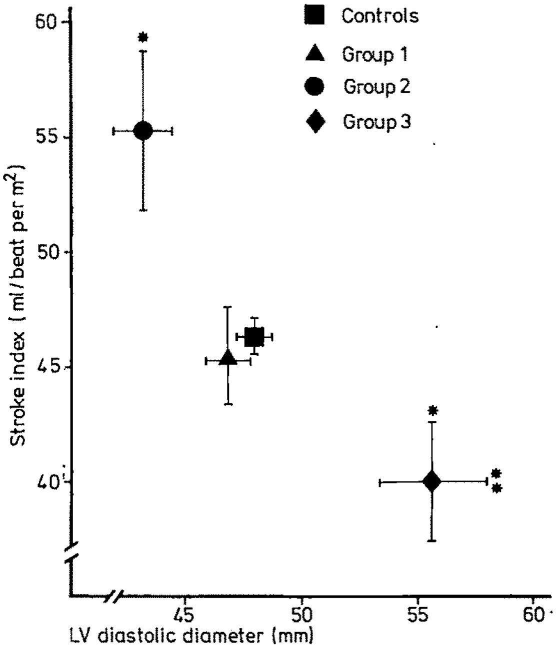

Fig. 3 *Relation between left ventricular diastolic diameter and stroke index in control subjects and hypertensive groups (mean ± SEM). * and ** indicate significance of differences from control group, with p values < 0·05 and < 0·01, respectively.*

Discussion

The accuracy of the echocardiographic method for measuring ventricular dimensions and wall thickness has been validated in previous reports.[8 12] It seems reasonable to consider that hypertensive groups in this study were characterised by actual differences in left ventricular structure. Several haemodynamic differences distinguish hypertensive from control subjects as well as one hypertensive group from another. Since the performance of the left ventricle results from interaction of preload, afterload, and contractility, the interplay of these factors should be considered whenever ventricular performance is assessed. Though preload is usually assessed by measuring ventricular diastolic pressure, changes in ventricular distensibility may render the diastolic pressure an unreliable guide to changes in diastolic volume or fibre length. In comparing hypertrophied and non-hypertrophied hearts, equality of ventricular diastolic pressure does not mean equality of initial fibre length because of the lesser distensibility of the hypertrophied heart; it has, in fact, been documented that wall thickness is an important determinant of left ventricular diastolic stiffness and pressure.[12] For these reasons the left ventricular end-diastolic diameter, rather than the diastolic pressure, was used to illustrate the Frank-Starling relation in Fig. 3. Upward displacement from normal in group 2 and downward displacement in group 3 of the stroke index-diastolic diameter relation indicate improved left ventricular function in the former group. Changes in contractility may account for these differences.

Circumferential fibre shortening (VCF) has been regarded by several investigators as a reliable index of the inotropic state of the myocardium.[13 14] The normal VCF in group 1, the increase in group 2, and the decrease in group 3 suggest that contractility is normal in group 1, increased in group 2, and reduced in group 3. However, before this interpretation is accepted, the influence of cardiac loading on VCF should be considered. It has been shown that VCF is affected minimally by changes in preload, but responds inversely to changes in afterload[15] so that changes in afterload may limit the clinical applicability of VCF as an index of contractility. When a low value of VCF is observed in a patient with increased afterload (left ventricular wall stress), the question arises whether this value reflects a reduced inotropic state of the myocardium, or results from a shift to a different point on a normal stress-velocity curve.

Circumferential wall stress is increased in groups 1 and 3 and reduced in group 2. However, because circumferential wall stress reflects the load on the left ventricle at the onset of systole, when fibre shortening does not occur, changes in wall stress cannot be related to changes in fibre shortening rate. For a more precise analysis, circumferential fibre shortening rate and wall stress should be measured continuously throughout the ejection phase. This would require high fidelity intraventricular pressure recordings made at the same time as continuous measurements of ventricular internal diameter and wall thickness; however, these measurements are not easily obtained particularly when a computer is not available. Our study does not provide this information and therefore leaves unanswered the question whether the increase in fibre shortening rate in group 2 and its reduction in group 3 are the result of changes in contractility, changes in wall stress, or both. It is likely that an increased velocity of fibre shortening, whatever its cause, is the mechanism by which rate of ejection and stroke index are increased in group 2 despite the higher pressure load and impedance to ejection (peripheral vascular resistance).

The functional capacity of hypertrophied myocardium has been the subject of considerable controversy.[16] Studies of hypertrophy produced experimentally by ventricular pressure overload, resulting from creation of aortic or pulmonary stenosis, have shown that myocardial contractility is decreased before the development of failure.[17 18] Other investigators found normal or improved ventricular function in animals with stable hypertrophy from either volume or pressure overload.[19–22] Skelton and Sonnenblick[23] have emphasised that changes in myocardial contractility in patients with cardiac hypertrophy are variable and depend upon the causative factor. Earlier reports[1–3] on hypertensive heart disease suggest that left ventricular function is impaired in the presence of hypertrophy, and the same conclusion was reached in a more recent assessment by Dunn and co-workers.[24] Our present findings, in agreement with those reported by Karliner and collaborators,[25] lead to different conclusions, and to a renewal of the controversy about the functional capacity of the hypertrophied myocardium arising from the results of animal experiments. The discrepancy probably results from the substantial difference between present criteria and earlier radiological and electrocardiographic criteria of left ventricular hypertrophy.[1–3 24]

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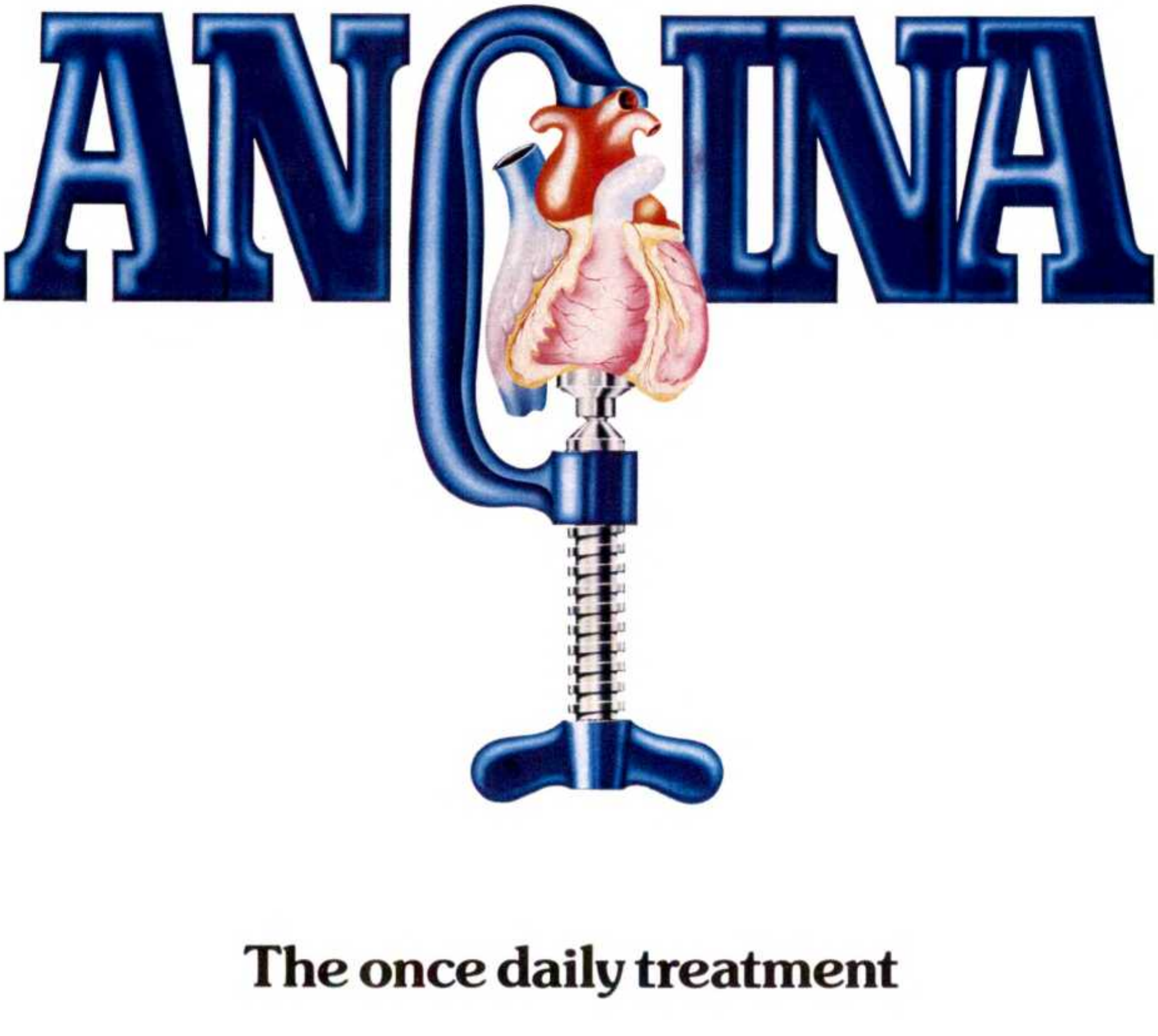

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Br Heart J 1980; **43**: 351–356

Two-dimensional echocardiographic diagnosis of aorticopulmonary window

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SUMMARY Two-dimensional echocardiography was performed in two cases of distal type aorticopulmonary window. The defect of the aorticopulmonary septum could be visualised in both cases in transverse section of the great arteries using our method. We make it a rule to study three different levels of section: plane 1, where the echo of the semilunar valve of the posterior great artery is well seen; plane 2, where the echo of the semilunar valve of the anterior great artery is clearly observed; and plane 3, where neither semilunar valve is seen. The aorticopulmonary septal defects were recognised at the level of plane 2 to plane 3 in our two cases. Two-dimensional contrast echocardiography was performed in one of the cases. The contrast entered the ascending aorta from the main pulmonary artery through the aorticopulmonary septal defect in early systole. Postoperatively, no defects were detected in the aorticopulmonary septum in either case using the same approach, and no passage of contrast into the ascending aorta from the pulmonary artery was noted in the case where contrast was injected. Accurate diagnosis of this anomaly can be made by visualisation of the defect utilising two-dimensional echocardiography. Typing of this anomaly, proximal, distal, or combined may be possible with our new approach.

Aorticopulmonary window is a relatively rare congenital anomaly involving the great arteries.[1–3] In patients with this defect, pulmonary resistance tends to increase during early infancy. Therefore, prompt and accurate diagnosis becomes mandatory. Aorticopulmonary window is now classified into three types, as documented previously.[4] The purpose of this paper is to report our new non-invasive approach to diagnosis of this defect using two-dimensional echocardiography.

Materials and methods

Instruments used for two-dimensional echocardiographic studies included a Toshiba Medical model SSH-10A phased-array ultrasonic sector scanner, an Hitachi Medico model EUB-10 phased-array sector scanner, and an Aloka model 110-S mechanical sector scanner.

Our routine approach when investigating spatial relation between the great arteries is as follows.[5] The probe is placed over either the third or fourth intercostal space. The semilunar valve of the posterior great artery is identified by M-mode echocardiography using a two-dimensional probe which is set as a single beam. The mode is then changed to real time while maintaining the axis of the probe; then a plane of the beam is rotated until a circular image of the great artery is obtained. This plane is designated plane 1, in which the echo of the semilunar valve of the posterior great artery is clearly seen. The echo plane is thereafter gradually directed cephalad, so that the echo of the semilunar valve of the anterior great artery is clearly obtained. This is designated plane 2. A slightly more cephalad plane, in which the echo of neither semilunar valve is shown, is designated plane 3. Pictures of normal great artery echoes in plane 1, plane 2, and plane 3 appear in Fig. 1. We studied two cases of aorticopulmonary window in which the diagnoses were confirmed at open surgical repair.

Case reports

CASE 1

A 3-year-old boy was admitted with a history of poor weight gain in infancy. Findings of combined ventricular hypertrophy on the electrocardiogram,

Received for publication 21 August 1979

pulmonary plethora with mild cardiomegaly, and bounding pulses indicated the presence of aorticopulmonary communication. The angiocardiogram is shown in Fig. 2. Contrast medium injected in the ascending aorta entered the right pulmonary artery predominantly. Two-dimensional echocardiographic findings are illustrated in Fig. 3. After cardiac catheterisation and confirmation of the lesion, repair was accomplished under direct vision. Preoperatively, the aorticopulmonary septum at the levels of plane 2 and plane 3 was shown to be deficient during the whole cardiac cycle by two-dimensional echocardiography. The aorticopulmonary window, measuring about 2 cm in diameter, was closed transaortically using a Teflon patch. After operation, the aorticopulmonary septum was

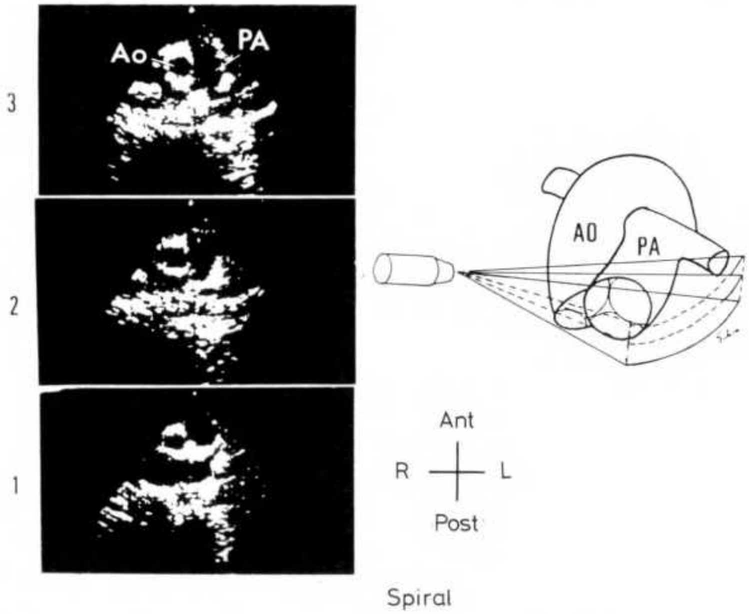

Fig. 1 *Two-dimensional echocardiographic findings of normal (spiral) relation between the great arteries. Posterior wall echo of the left anterior great artery is extended posteriorly from plane 1 to plane 3 (see text). Left-sided structures are to the right and right-sided structures are to the left of the observer. Ao, aorta; PA, pulmonary artery.*

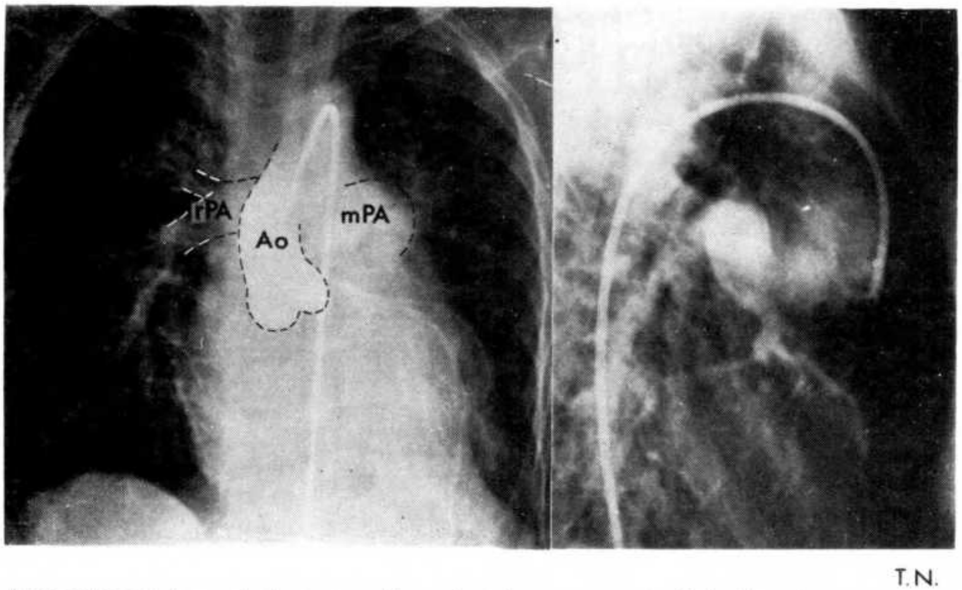

Fig. 2 *Angiocardiogram in case 1. Ao, aorta; mPa, main pulmonary artery; r-PA, right pulmonary artery.*

clearly seen even in plane 2 to plane 3 by two-dimensional echocardiography (Fig. 4).

CASE 2

A 3-year-old boy was referred to us with a diagnosis of left-to-right shunt and pulmonary hypertension. The electrocardiogram showed combined ventricular hypertrophy and a chest *x*-ray film showed mild cardiomegaly with pulmonary hypervascularity. Cardiac catheterisation showed pulmonary arterial pressure equivalent to systemic pressure. The angiocardiogram, with right ventricular outflow tract and aortic root injections, is shown in Fig. 5 and 6. Contrast medium injected at the aortic root shows preferential opacification of the right pulmonary artery indicating a distal type of aorticopulmonary window.[4] Contrast medium injected in the right ventricular outflow tract opacifies the main pulmonary artery, both pulmonary arteries, and the descending aorta. The data from catheterisation and the angiograms, shown in Fig. 5 and 6, indicate a distal type of aorticopulmonary window with interruption of the aorta (type A). M-mode echocardiography showed no specific findings. Two-dimensional echocardiographic findings are shown in Fig. 7. The echo of the aorticopulmonary septum was absent at the levels of plane 2 and plane 3 preoperatively. During this examination, contrast echocardiography was performed. Glucose (1 ml of 5 per cent) was injected into the right antecubital vein while viewing plane 3 by two-dimensional echocardiography. The contrast medium entered the main pulmonary artery through the right ventricular outflow tract and entered the aorta via the aorticopulmonary septal defect in early systolic phase (Fig. 8). However, at the level of plane 1, no contrast was seen flowing from the right ventricular outflow tract to the ascending aorta. A patch closure of the aorticopulmonary window (measuring 1·5 cm in diameter) was carried

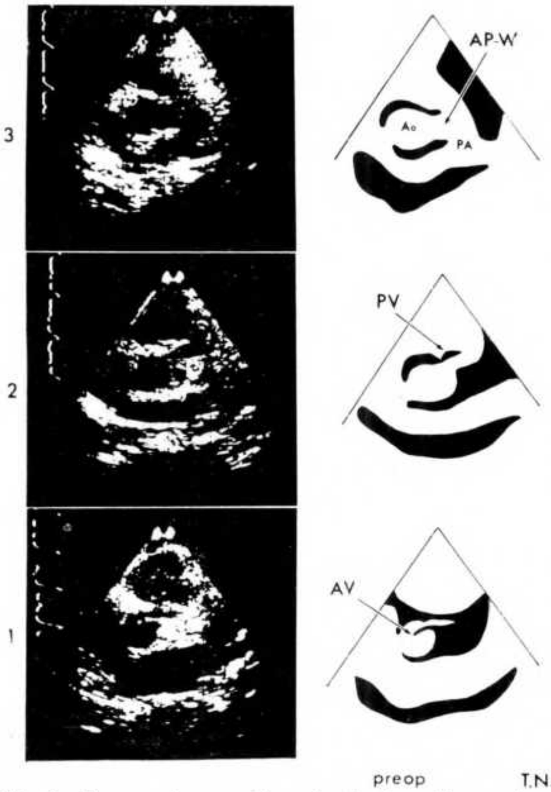

Fig. 3 *Preoperative two-dimensional echocardiogram in case 1. AV, aortic valve; PV, pulmonary valve; Ao, aorta; PA, pulmonary artery; AP-W, aorticopulmonary window.*

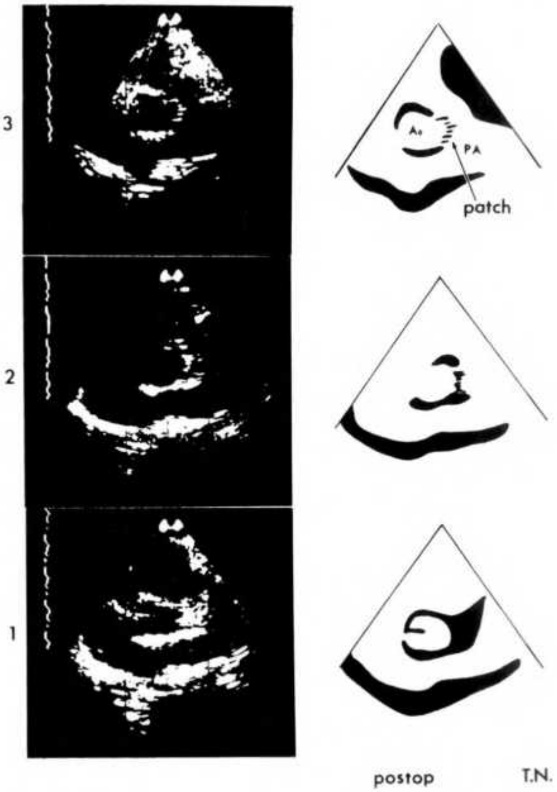

Fig. 4 *Postoperative two-dimensional echocardiogram in case 1. Ao, aorta; PA, pulmonary artery; patch, patch echo.*

out successfully by transaortic approach; anastomosis of the aortic arch to the descending aorta was accomplished using an artificial graft. Postoperatively, two-dimensional echocardiography was performed again. No defect of the aorticopulmonary septum was seen at any level (Fig. 9). Two-dimensional echocardiography with contrast was also performed by peripheral vein injection. No contrast echo was detected moving from the main pulmonary artery to the ascending aorta.

Discussion

A two-dimensional echocardiographic diagnostic approach using three differential planes is very useful for identifying the pulmonary artery and the

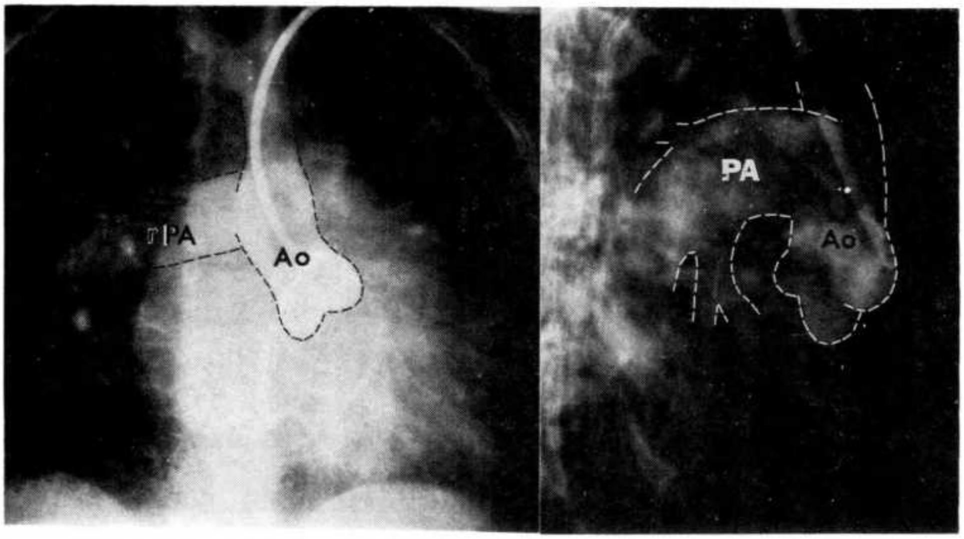

Fig. 5 *Angiocardiogram in case 2 with aortic root injection. Ao, aorta; r-PA, right pulmonary artery.*

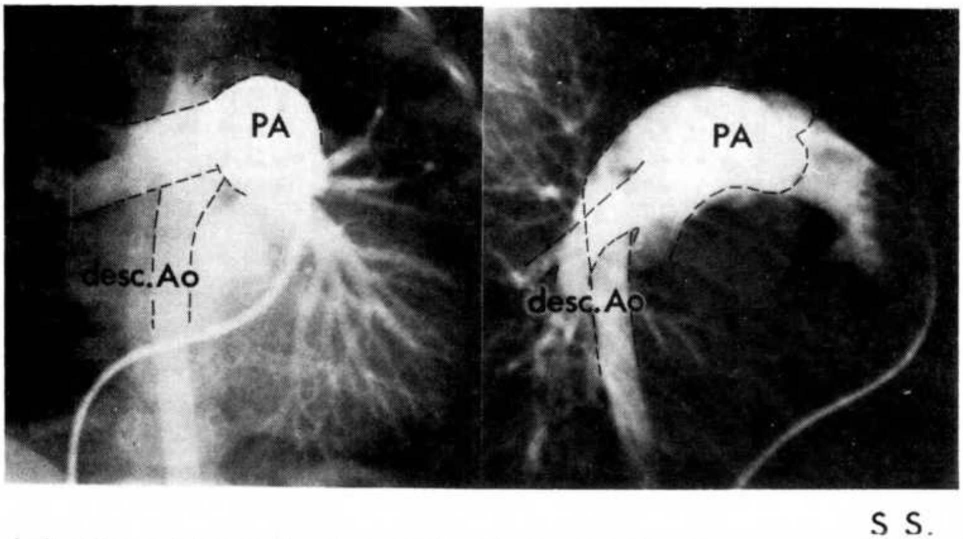

Fig. 6 *Angiocardiogram in case 2 with right ventricular outflow injection. PA, pulmonary artery; Ao, descending aorta.*

aorta, and for recognising spatial relations between them.[5] [6] Aorticopulmonary septal defect was visualised by two-dimensional echocardiography at the level of plane 2 to plane 3 in both cases with distal type aorticopulmonary window.

A portion of the circular aortic echo which is

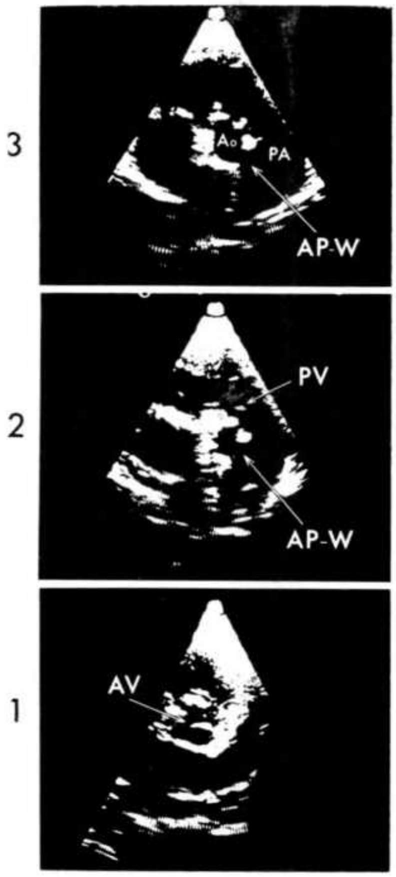

Fig. 7 *Preoperative two-dimensional echocardiographic findings in case 2. AV, aortic valve; PV, pulmonary valve; AP-W, aorticopulmonary window.*

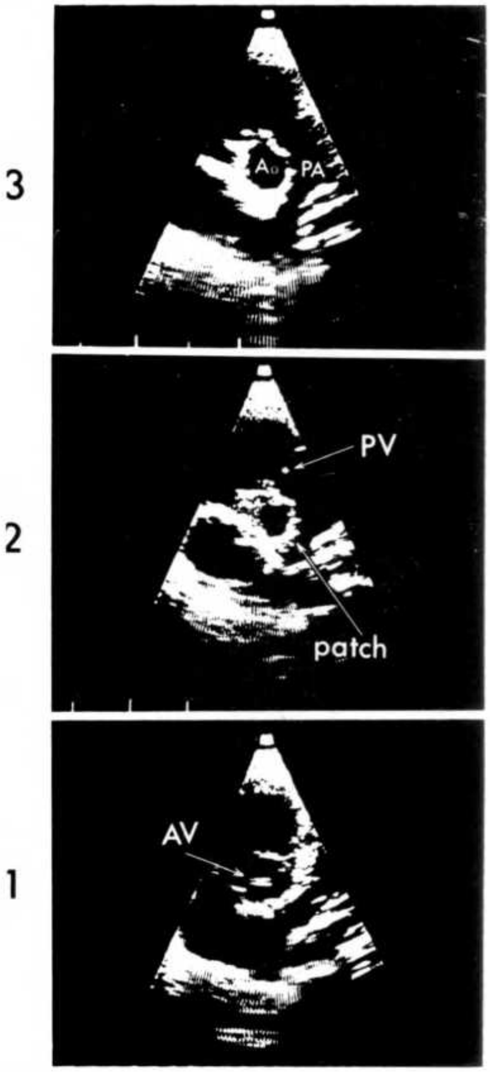

Fig. 9 *Postoperative two-dimensional echocardiographic findings in case 2. AV, aortic valve; PV, pulmonary valve; Ao, aorta; PA, pulmonary artery; patch, patch echo.*

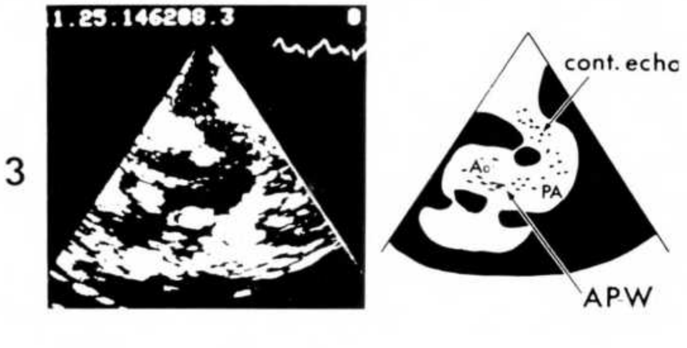

Fig. 8 *Preoperative contrast two-dimensional echocardiographic record in case 2 showing the contrast entering the aorta from the main pulmonary artery. Cont. echo, contrast echo; AP-W, aorticopulmonary window.*

parallel to ultrasonic beams may appear as drop-out effect, even in normal subjects, especially on stop-action frames. However, use of real-time images alleviates these problems according to the human capability for integration,[7] and no drop-out was observed in the normal subjects in plane 2 to plane 3 and real-time two-dimensional echocardiography. In the two cases reported here, relatively large echo defects of a portion of the aorticopulmonary septum were observed during the whole cardiac cycle even on real-time two-dimensional echocardiography. Other evidence of the defect is the passage of the contrast echo from the pulmonary artery to the ascending aorta. Two-dimensional contrast echocardiography was performed in one case. Contrast was noted passing through the aorticopulmonary septal defect at the level of plane 3; this phenomenon was missed at the level of plane 1. An aorticopulmonary window was found at the level of plane 2 to plane 3, and not at the level of plane 1. Accordingly, in a case with the proximal type of aorticopulmonary window, we expect to find the defect only at the level of plane 1 or slightly cephalad to it. When the defect is as described in the two cases reported here, it may be seen at the level of plane 2 to plane 3, and, in the combined proximal and distal type, two-dimensional echocardiographic study will probably show the defect in all planes. We hope to substantiate this speculation by further experience with such cases.

The operative approach, transpulmonary or transaortic, should be chosen according to the type of aorticopulmonary window.[4] Therefore, accurate diagnosis and typing of this anomaly must be made before operation. Two-dimensional echocardiography can be a very useful non-invasive diagnostic tool in aorticopulmonary window.

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Br Heart J 1980; **43:** 357–359

Surgical treatment of endomyocardial fibrosis with preservation of mitral valve

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SUMMARY A 48-year-old Kenyan African, who presented with a history of coronary and cerebral embolism, was found to have endomyocardial fibrosis of the left ventricle. It proved possible to remove all diseased tissue at operation, and at the same time to preserve the mitral valve. It is important to inspect the mitral valve from both the atrial and ventricular aspects so that the valve can be spared, if it is not involved in the disease process. The choice of transatrial of transventricular surgical approach for the removal of pathological tissue may depend on whether or not the mitral valve requires replacement.

In the disorder of unknown aetiology known as endomyocardial fibrosis (Bedford and Konstam, 1946) surgical treatment may be required. This was first carried out successfully on the left ventricle by Lepley *et al.* (1974). In published cases, it has always been necessary to replace the mitral valve when left ventricular lesions have been surgically resected. We report an early case in which we were able to preserve the mitral valve apparatus, and describe the technique that permitted this to be achieved.

Case report

A 48-year-old Kenyan African presented with a well-documented history of acute anterior myocardial infarction in October 1973. After this he had occasional dyspnoea and angina pectoris and in March 1977 a transient left hemiparesis.

On examination in July 1977 he looked well; the pulse was regular at 70 beats per minute and the blood pressure was 130/80 mmHg. The venous pressure was not raised and the left ventricular impulse was normal. There was a soft midsystolic murmur at the apex and there were quiet third and fourth heart sounds. The rest of the physical examination was normal.

The electrocardiogram showed broad P waves, left axis deviation, right bundle-branch block, and deep Q waves in V1 to V5; there was also T wave inversion without ST elevation in aVL and V1 to V4. A chest *x*-ray film showed a bulge on the left border of the heart. Haemoglobin and white cell count were normal. Tests for auto antibodies to nuclear protein, smooth muscle, reticulin, and mitrochondria were negative. Blood urea, electrolytes, and liver function tests were normal. At cardiac catheterisation, the left ventricular end-diastolic pressure was 30 mmHg and the left ventricular angiogram showed a large filling defect at the apex (Fig.), with anterior dyskinesia but no abnormality of the mitral valve. Coronary arteriograms were normal.

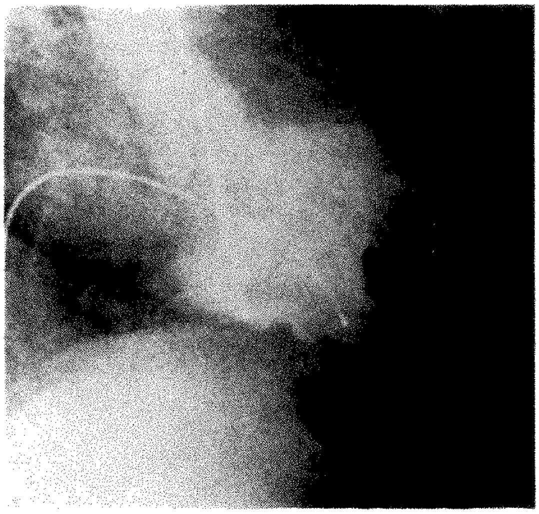

Fig. *Left ventriculogram (30° RAO) showing apical filling defect.*

A provisional diagnosis of endomyocardial fibrosis was made, but because of the uncertainty about the precise diagnosis, and the possibility that the transient hemiplegia was the result of embolisation of mural thrombus, operation was advised. This was carried out under cardiopulmonary bypass and hypothermia (30°C) by Professor H. H. Bentall. The external appearance of the fat-laden apex was normal, but an area of fibrosis 5 × 5 cm could be felt beneath it. The mitral valve was normal on inspection through the left atrium. With the aorta cross-clamped, the left ventricular apex was opened by a curved incision. The fibrous tissue, which was 1·5 cm thick at its centre and thinner towards the periphery, was loosely attached to the underlying myocardium, providing a good plane of cleavage. Thrombus was loosely attached to the endocardial aspect of the fibrous tissue. There was a gap of about 1 cm between the edge of the fibrosis and the base of the papillary muscles, and no skip lesions. The diseased area was dissected off completely leaving both papillary muscles intact. The ventriculotomy was closed and the bypass terminated.

After the operation the systolic murmur was no longer audible. He made an uneventful recovery and was discharged two weeks later taking aspirin (600 mg daily). When he was seen in the out-patient clinic 12 months later, he was well and symptom free, and it was considered unjustified to repeat the angiogram.

Histological examination (Dr J. Hoffa) showed the characteristic changes of endomyocardial fibrosis. There was partially organised blood clot with fibrin and dilated capillaries on the endocardial surface and also young fibroblasts and macrophages. Deep to this layer there was a broad zone of acellular hyalinised fibrous tissue. Adjacent to the myocardium the fibrous tissue was more cellular with some dilated vessels which entrapped superficial myocardial fibres.

Discussion

In this patient myocardial tumour and thrombus overlying previous infarct were considered in the differential diagnosis. Tumour seemed unlikely in the absence of a pathological circulation in the angiogram. The extensive myocardial infarct could not be attributed to coronary atherosclerosis in the presence of a normal coronary arteriogram, and was probably the result of coronary embolus. In addition, the hemiplegia was best explained by cerebral embolism. The systolic murmur was probably caused by papillary muscle dysfunction which was corrected by the operation. The operation was carried out because of the uncertainty about the precise diagnosis and the fear of further emboli.

The exact cause of endomyocardial fibrosis remains uncertain. The right ventricle is more frequently involved than the left (Shillingford and Somers, 1961) and the apex and inflow tracts of the ventricles are predominantly affected (Davies and Ball, 1955; Shaper, 1972): the atrioventricular valves usually become regurgitant because fibrosis binds the papillary muscles to the endocardium (Farrer-Brown and Tarbit, 1972). Endomyocardial fibrosis of the left ventricle may present with mitral regurgitation, pulmonary hypertension, or systemic embolism, and the preoperative diagnosis depends on angiography. No drugs are known to arrest or reverse this disease; survival after diagnosis varies from 12 days to 12 years, with a mean of two years (D'Arbela *et al.*, 1972).

Several further reports have appeared since the first successful excision of endomyocardial fibrosis of the left ventricle (Lepley *et al.*, 1974); in all cases, the mitral valve has been replaced. Our case shows that the mitral valve can be preserved if the disease does not involve it. Lesions of the ventricle can be resected through either the left atrium (Dubost *et al.*, 1976) or the left ventricle (Lepley *et al.*, 1974). Using the transatrial approach the mitral apparatus is excised as the first step. The technical advantage of this approach is the ease of inserting sutures in the mitral ring from above. It does, however, deprive the surgeon of the opportunity to conserve the mitral valve. The second approach has the advantage that the left ventricular apex and the bases of the papillary muscles are adequately exposed and the mitral valve can be spared when possible. It is, however, less easy to inspect and replace the valve by the ventricular approach. In order to identify those cases in which the mitral valve can be preserved, the valve should be examined from the left atrium, and, if it does not need replacement, the operation should be continued through a left ventriculotomy.

We thank Professor H H Bentall, Professor J F Goodwin, and Dr J B O Okanga for permission to report this case.

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Requests for reprints to U Nair, Esq., FRCS, Department of Cardiothoracic Surgery, Royal Postgraduate Medical School, Du Cane Road, London W12 0HS.

Br Heart J 1980; **43:** 360–362

Echocardiographic diagnosis and successful removal of cardiac fibroma in 4-year old child

P C ETCHES,* B GRIBBIN, A J GUNNING

From the Department of Paediatrics, the Department of Cardiology, and the Nuffield Department of Surgery, The Radcliffe Infirmary, Oxford

SUMMARY An intramyocardial fibroma shown by echocardiography and angiocardiography was removed from the apex of the left ventricle of an asymptomatic 4-year-old boy.

Primary cardiac tumours are rare and Simcha *et al.* (1971) found an incidence of 0·08 per cent of all cases of congenital heart disease seen at The Hospital for Sick Children, Great Ormond Street. Fibromas or fibro-hamartomas comprise less than 10 per cent overall (Griffiths, 1965) and occur mostly in children (Geha *et al.*, 1967). The first successful removal of a cardiac fibroma was reported by Parks *et al.* in 1962, since when this procedure has been more frequently attempted. We report the use of echocardiography to diagnose a left ventricular fibroma in a 4-year-old boy and its subsequent surgical removal.

Case report

A 4-year-old boy was admitted for investigation when a routine chest *x*-ray film, taken because he was a tuberculosis contact, showed distinct cardiomegaly. His previous history was unremarkable, except that during the two weeks before admission he had lost consciousness on two occasions. Physical examination was normal but the electrocardiogram showed T wave inversion in the anterolateral leads, and echocardiography disclosed gross thickening of the posterior wall of the left ventricle (Fig. 1). At cardiac catheterisation, intracardiac pressures were normal but angiography showed a filling defect at the apex of the left ventricle.

At operation, a hard mass, approximately 60 ×

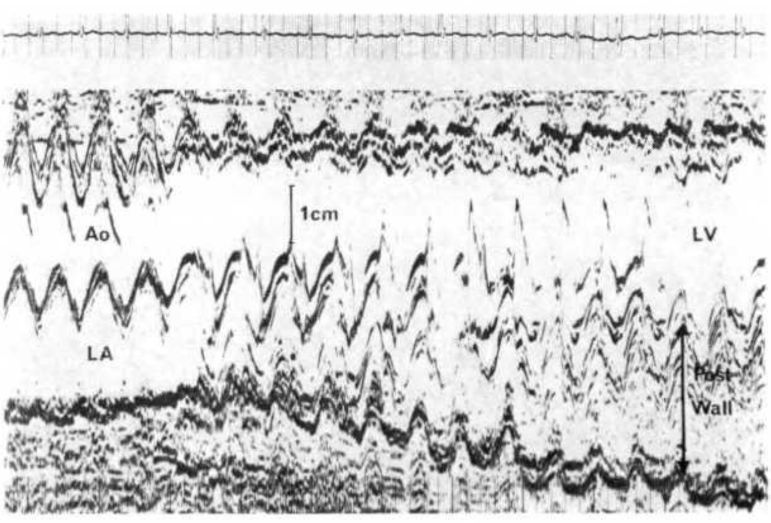

Fig. 1 *M-mode single crystal echocardiographic sweep from the aortic root to the left ventricle. The posterior wall is grossly thickened.*

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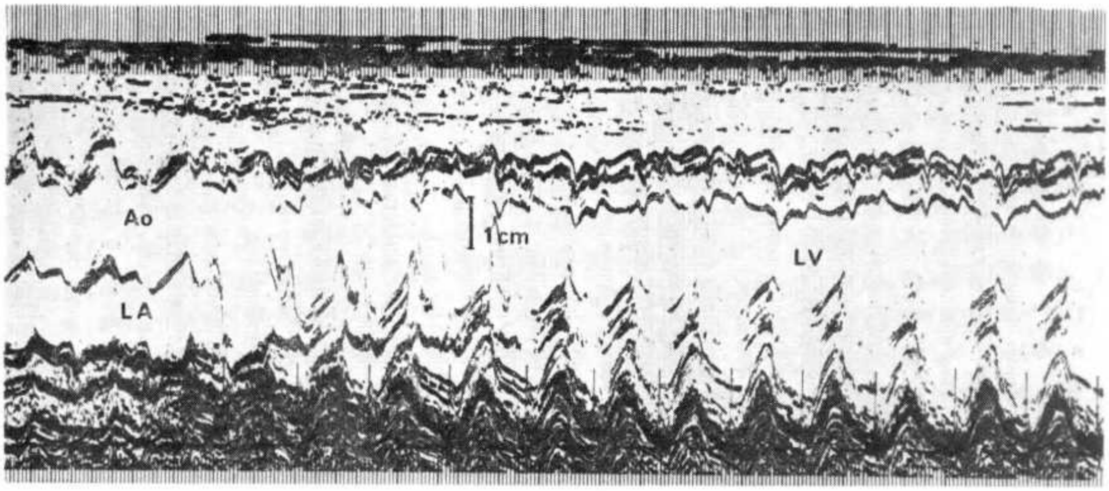

Fig. 2 *Twenty-one months after operation the appearances are normal.*

45 mm, was found occupying the posterolateral aspect of the apical portion of the left ventricle. Frozen sections of biopsies from the mass had the appearance of a benign fibroma. The patient was then put on to bypass and the tumour enucleated from the myocardium with the aid of sharp dissection. Closure of the resultant defect in the myocardium did not reduce the left ventricular volume and the heart was beating throughout the procedure.

The removed specimen was a rubbery greyish white tumour weighing 43 g and measuring 58 × 48 × 35 mm. The cut surface had a whorled appearance with two or three calcified foci up to 2 mm in diameter. There was no true capsule and the histological appearances were typical of a benign intramyocardial fibroma. Postoperative recovery was satisfactory and a repeat echocardiogram showed apparently normal left ventricular dimensions (Fig. 2).

Discussion

The general clinical and pathological features of cardiac fibromas have been fully reviewed elsewhere (Geha *et al.*, 1967; Soler-Soler and Romero-Gonzalez, 1975). Our patient had none of the commonly reported symptoms such as cardiac failure or palpitation though it is possible that the episodes of unconsciousness were initiated by a syncopal attack. Certainly there has been no recurrence postoperatively. The chest *x*-ray film showed a characteristic cardiomegaly but no tumour calcification was seen though this is commonly present (Soler-Soler and Romero-Gonzalez, 1975). Electrocardiographic changes of T wave depression which have been well described in cases of fibroma (Thomsen *et al.*, 1971; Waaler *et al.*, 1972) were also seen in our patient, but echocardiography provided the most striking demonstration of the tumour. There have been several reports outlining the usefulness of echocardiography in the diagnosis of cardiac tumours (Allen *et al.*, 1974; Farooki *et al.*, 1974) but angiography as in this case seems to offer the best chance of defining the position and extent of the lesion.

Cardiac fibromas have been comprehensively reviewed by Geha *et al.* (1967), and more recently by Fouchard *et al.* (1972) who described 58 patients with this form of tumour. Since this review further case reports have appeared giving a total of 79 patients, 65 of whom were children and in 41 of whom an attempt at tumour excision was made with 13 deaths, a mortality rate of 32 per cent. The natural history of these lesions is not known but since the majority present clinically in childhood and the tumour is a rare finding in adults at necropsy, it seems that very few remain completely silent. Though it is a benign, slow growing tumour, it may well produce lethal effects by interference with the conducting system or by causing outflow obstruction to either ventricle. We therefore conclude that the risks of surgery are usually justified.

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Br Heart J, 1980; **43**:363–365

Single origin of right and left pulmonary arteries from ascending aorta, with main pulmonary artery from right ventricle

ALBRECHT BEITZKE AND ELLIOT A SHINEBOURNE

From the Departments of Paediatric Cardiology, The Children's Hospital, University of Graz, Austria, and the Brompton Hospital, London

SUMMARY A previously undescribed anomaly is presented in which right and left pulmonary arteries arise via a single vessel from the ascending aorta while the main pulmonary artery arises normally from the right ventricle. This main pulmonary artery has no branches supplying the lungs and connects via a ductus arteriosus to the descending aorta. Additional anomalies were an atrial septal defect and tubular hypoplasia of the aortic isthmus.

This baby boy was the first child of a 28-year-old healthy woman. The pregnancy was uneventful; caesarean section was performed because of small pelvis and postmaturity. The baby required resuscitation after birth. Arterial blood gases from an umbilical arterial catheter one hour after birth showed normal *p*H and P_{CO_2} but a P_{O_2} of 36 mmHg. At 13 hours the baby was referred to the Children's University Hospital, Graz, because of persistent cyanosis, hepatomegaly, and tachypnoea. On admission there was central cyanosis, tachypnoea up to 80/minute, and 2 cm hepatomegaly. The heart rate was 180/minute, there was a loud pulmonary component to the second sound, and a grade 3/6 ejection systolic murmur maximal at the second left intercostal space. All pulses were easily palpable and equal with a systolic pressure of 60 mmHg. *p*H was 7·4, P_{CO_2} 40 mmHg, P_{O_2} breathing 100 per cent O_2 60 mmHg, Hb 16·3 g/dl, haematocrit 60 per cent.

The chest *x*-ray film showed cardiac enlargement with increased pulmonary vascular markings. Electrocardiogram showed sinus rhythm, mean frontal QRS axis +150°, and right ventricular hypertrophy. At cardiac catheterisation there were equal atrial pressures. Right ventricular and pulmonary arterial systolic pressures were 105 mmHg compared with 75 mmHg in the left ventricle and aorta. The catheter passed from the right ventricle to the pulmonary trunk and to the descending aorta via a ductus arteriosus. It was not possible to enter branches of the main pulmonary artery. A Swan Ganz catheter was manipulated from the left ventricle into the ascending aorta and into a large vessel originating from its posterior aspect. A left ventriculogram (Fig. 1a and b) showed a normal left ventricle from which arose the aorta. There was a left aortic arch. Arising from the posterior aspect of the ascending aorta was a short single vessel that divided into right and left pulmonary arteries. The right ventricular injection showed this chamber to be normal (Fig. 2a) while neither of the ventricular injections demonstrated a ventricular septal defect. An anterior main pulmonary artery arose anteriorly from the right ventricle but no right or left pulmonary arteries arose from it. The main pulmonary artery continued as a narrowed ductus arteriosus (Fig. 2b and 3), both arterial valves were outlined, and moderate aortic isthmal narrowing was seen. The full diagnosis was situs solitus with atrioventricular and ventriculoarterial concordance, atrial septal defect, hypoplastic aortic isthmus, and abnormal origin of a vessel arising from the ascending aorta supplying right and left pulmonary arteries. The infant's condition deteriorated. Surgery was attempted on the 11th day of life. The vessel arising from the ascending aorta was dissected and connected with the solitary pulmonary trunk arising from the right ventricle. The ductus was ligated and divided. The infant did not come off bypass and died. Necropsy confirmed the angiographic diagnosis.

Discussion

In contrast to the aberrant origin of one pulmonary artery from the ascending aorta either as an isolated anomaly (Sanger *et al.*, 1965; Winship *et al.*, 1967; Kuypers *et al.*, 1969; Keane *et al.*, 1974) or in association with intracardiac defects (Flege *et al.*, 1970; Kuers and McGoon, 1973; Keane *et al.*,

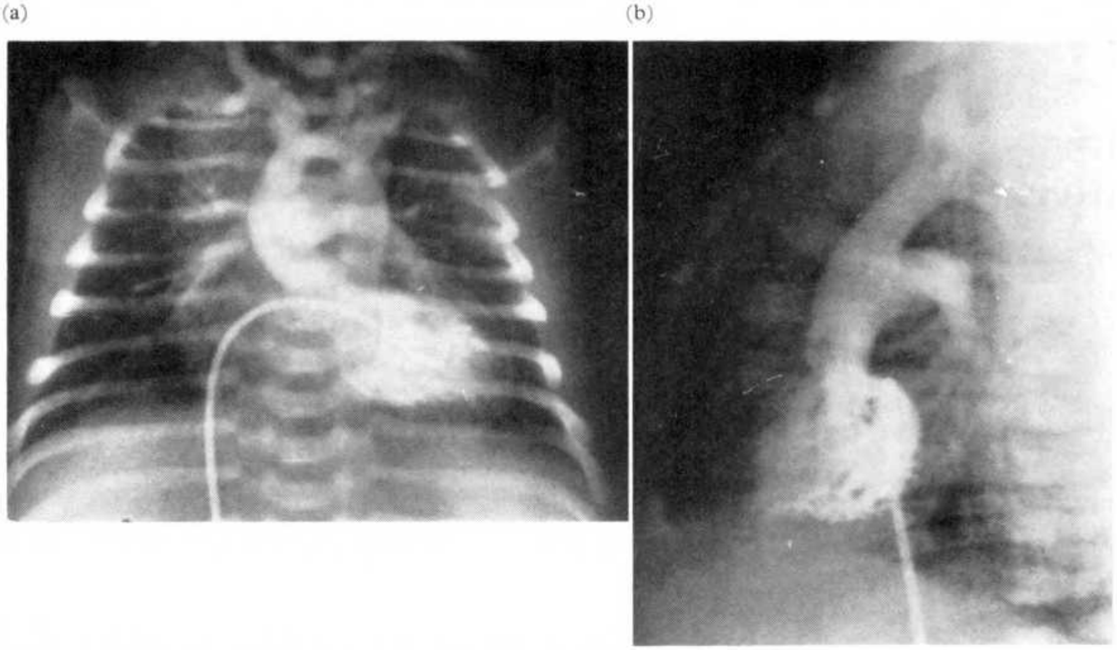

Fig. 1a and b *Left ventricular injection showing a large vessel supplying right and left pulmonary arteries arising from the posterior aspect of the ascending aorta. An intact interventricular septum, left aortic arch, and moderate coarctation can also be seen.*

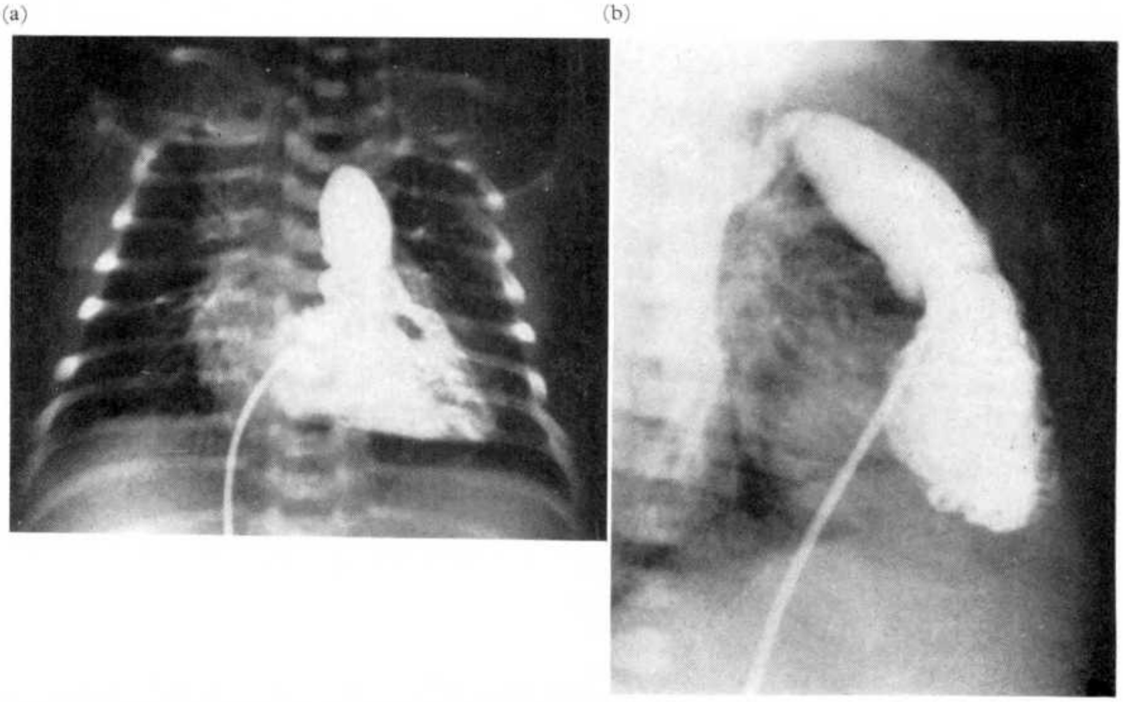

Fig. 2a and b *Right ventricular injection showing a large right ventricle and main pulmonary trunk without pulmonary artery branches to the lungs. Opacification of ascending aorta via a persistent ductus arteriosus.*

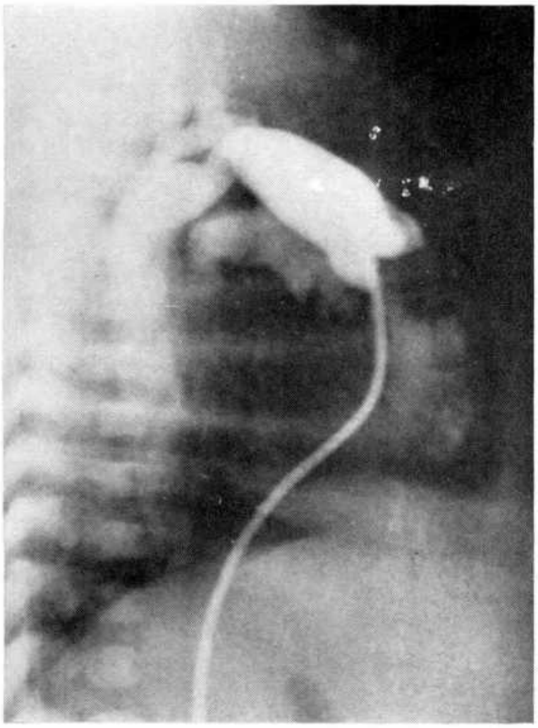

Fig. 3 *Injection into the pulmonary trunk showing both aortic and pulmonary valves, with the abnormal vessel arising from ascending aorta and a hypoplastic isthmus.*

1974), this anomaly has not to our knowledge been previously described.

Any embryological explanation for its anatomy is speculative. In the normal heart the pulmonary trunk is derived primarily from septation of the truncus arteriosus while the intrapulmonary vessels develop *in situ*. Later during development the proximal part of the left sixth aortic arch is adsorbed into the wall of the pulmonary trunk while its distal part persists as the ductus arteriosus. Thus the definitive left pulmonary artery is derived solely from intrapulmonary vessels. In contrast the right main pulmonary artery is derived from the proximal part of the right sixth aortic arch, the distal portion of which normally undergoes involution. The intrapulmonary vessels normally join the paired sixth aortic arches at the junction of their proximal and distal parts. Septation of the truncus arteriosus is by two bulbotruncal ridges, abnormal orientation of which has been suggested as the basis for origin of the right pulmonary artery from the ascending aorta (Cucci *et al.*, 1964). In all examples of this latter group, however, the pulmonary trunk gave rise to the left pulmonary artery. When a left-sided ductus arteriosus was present as well (Sanger *et al.*, 1965; Winship *et al.*, 1967; Kuypers *et al.*, 1969; Keane *et al.*, 1974) the complete left sixth aortic arch appears to have persisted.

Our case differs from these in that the left-sided intrapulmonary artery has no connection to the pulmonary trunk. A possible explanation for this is that the vessel arising dorsally from the ascending aorta represents the proximal part of the right sixth aortic arch in normal connection with the right intrapulmonary vessels. The complete left sixth arch is present as part of the pulmonary trunk and persistent ductus arteriosus. The left-sided intrapulmonary vessels however have come into abnormal connection with the proximal right sixth arch. There is some evidence for this theory. In our patient the right pulmonary artery appears shorter and the left pulmonary artery longer and more horizontal than in the normal (Fig. 1a). This could reflect failure of leftward migration of the proximal right sixth arch and excessive rightward migration of the left-sided intrapulmonary vessels.

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Correspondence

Br Heart J 1980; **43:** 366

Sarcoid heart disease

Sir,
I read with interest the exchange of letters between Johnson *et al.* and Walsh (*Br Heart J* 1979; **42:** 367). I must agree with Walsh that a negative myocardial biopsy in no way rules out the diagnosis of sarcoid heart disease. I know of only one positive biopsy in this country and few elsewhere in the world. I now have personal detailed knowledge of about 50 necropsied hearts with sarcoid heart disease and, knowing the patchy distribution of the lesions in most cases, I am not surprised at the negative biopsy and would accept both of Johnson's patients as cases of sarcoid heart disease until proved otherwise. We have seen very similar cases being confirmed at necropsy.

My current criteria for the inclusion of a case in my continuing study are: (1) cardiac condition compatible with sarcoidosis; (2) no other explanation for heart disease; (3) positive diagnosis of sarcoidosis[1] preferably with histology.

On this basis I would welcome full details of Johnson *et al.*'s patients so that I might add them to our collective experience.

I continue to be surprised at the reluctance to diagnose sarcoid heart disease even at necropsy, and a recent case exemplifies this.

A 52-year-old woman, who developed heart block with cardiomegaly, was paced for 10 months before death. Skin biopsy was positive for sarcoidosis and the medical opinion, including my own, was that this should be regarded as sarcoid heart disease. When she died suddenly a coroner's necropsy was carried out. The heart weighed 670 g and, macroscopically, there was extensive fibrosis in both ventricles. It was noted specifically that there was minimal coronary artery disease and yet the cause of death was recorded as 'ischaemic heart disease'. No histological examination was made of the heart, though the sections of the lungs and lymph nodes were reported as showing 'tuberculosis'. Review of sections of lung and spleen by another pathologist gave the diagnosis of sarcoidosis. I feel, therefore, that this patient should still be included in my series as almost certainly a case of sarcoid heart disease.

Short of adequate necropsy examination or positive myocardial biopsy, it is impossible to be sure of the diagnosis of sarcoid heart disease. My collection of cases, however, shows that it is not rare and yet until our reports there was only a single case report[2] in a United Kingdom journal. Silverman *et al.*[3] at Johns Hopkins studied 84 necropsy patients with sarcoidosis and reported that in at least 25 per cent there was myocardial involvement. The true incidence is probably higher.[4]

It has been reported by Kinney *et al.*[5] that thallium myocardial perfusion scanning is of value in assessing sarcoid disease of the heart and we suggest that this should be added to 24-hour electrocardiographic monitoring, echocardiography, and possibly the estimation of angiotensin converting enzyme in the investigation of these patients.

I do not intend to venture an opinion on the difficult question of treatment, to which I referred at the British Cardiac Society Meeting in 1978, but, like Walsh, I hope that the long-term follow-up of a collection of all possible cases will eventually give us more information about this.

Hugh A Fleming,
Papworth Hospital,
Papworth Everard,
Cambridge.

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[4] Fleming HA. Cardiac sarcoid. *Circulation* 1979; **59:** 1336.

[5] Kinney EL, Jackson GL, Reeves WC, Zelis R. The prevalence of sarcoid heart disease detected by thallium scanning. *Am J Cardiol* 1979; **43:** 437 (Abst.).

Br Heart J 1980; **43**: 367

Ventricular ectopy

Sir,
The proceedings of the British Cardiac Society (*Br Heart J* 1979; **41**: 360–384) include one abstract in which 'ventricular ectopy' is the subject. It was particularly disappointing to see this in the *British Heart Journal* as I felt quite certain that 'ectopy' was an unfortunate neologism both coined in and confined to the United States of America. Our dictionaries, both medical and general, define 'ectopy' or 'ectopia' as something which is found in the wrong place—usually a congenital calamity (I do not know about the OED). This subject has been dealt with in detail elsewhere for both this and other vogue words.[1] I hope that this single linguistic aberration is not the initial sign of transatlantic contagion. Many of us here draw comfort from the notion that whatever the local assaults on the English tongue its guardians in London remain on the job.

David H Spodick,
University of Massachusetts
Medical School, and
Division of Cardiology,
St. Vincent Hospital,
Worcester, Mass, USA.

Reference

[1] Spodick DH. Vogue words—ectopic language. *JAMA* 1978; **240**: 2439–40.

Editorial note

It is true that we stared suspiciously at ectopy for a few days before passing it. We had heard it used over the past few years by all ranks of cardiological societies in many countries and frankly thought it served a purpose. If the beats were ectopic, how were we to describe in a word the occurrence of frequent ectopic beats? Seeing it in print, however, we have second thoughts and we are disturbed by Dr Spodick's protest because we share his aversion to vogue words. Yet, if not ectopy, what? In the meantime, Dr Spodick and other well-wishers may be assured that we are committed to do our best to avoid offensive neologisms.

Notices

Br Heart J 1980; **43**: 368

European Society of Cardiovascular Surgery

The 29th international congress of the European Society of Cardiovascular Surgery (ESCVS) will be held from 2 to 5 July 1980 in Düsseldorf (West Germany).

Detailed information may be obtained from: Professor Dr W Bircks, Chirurg. Univ. Klinik B, Moorenstrasse 5, D-4000 Düsseldorf, Germany.

Italian Society of Paediatric Cardiology

Xth Congress of Italian Society of Paediatric Cardiology will be held in Padova, Italy, on 2–4 May 1980. For further information, contact: Dr Gaetano Thiene, Istituto di Anatomia Patologica, Via Gabelli 61, 35100 Padova, Italy.

Cardioplegia

An international symposium organised by St. Thomas' Hospital and the Royal Postgraduate Medical School at The Royal Society, 6 Carlton House Terrace, London SW1, on 9 and 10 June 1980.

Further information from Advisory Services Medical Symposia, 79 Wimpole Street, London W1.

Meetings Sponsored By the European Society of Cardiology in 1980

27–30 April, Dubrovnik, Yugoslavia. International symposium on non-invasive methods.

Inquiries to Prof F Loogen, Med. Klinik B—Kardiologie Universität Düsseldorf, Moorenstrasse 5, D—4000 Düsseldorf, Germany.

25–28 September, Bruges, Belgium. Function of cardiovascular afferent nerves.

Inquiries to Prof H Denolin, 178 avenue Winston Churchill, Bte 10, 1180 Bruxelles, Belgium.

20–30 October, Athens, Greece. Epidemiology of atherosclerosis.

Inquiries to Dr D. Athanassiades, President, Hellenic Cardiological Society, 17 Sissini Street, Athens 612, Greece.

1–2 December, Antwerp, Belgium. Prostaglandins and the vascular wall.

Inquiries to Prof H Denolin, 178 avenue Winston Churchill, Bte 10, 1180 Bruxelles, Belgium.

Supplement to BRITISH HEART JOURNAL

PREVENTION OF ARRHYTHMIAS

The Proceedings of a Symposium held at Freeman Hospital, Newcastle upon Tyne, on 12 and 13 September 1977, arranged by Professor D G Julian

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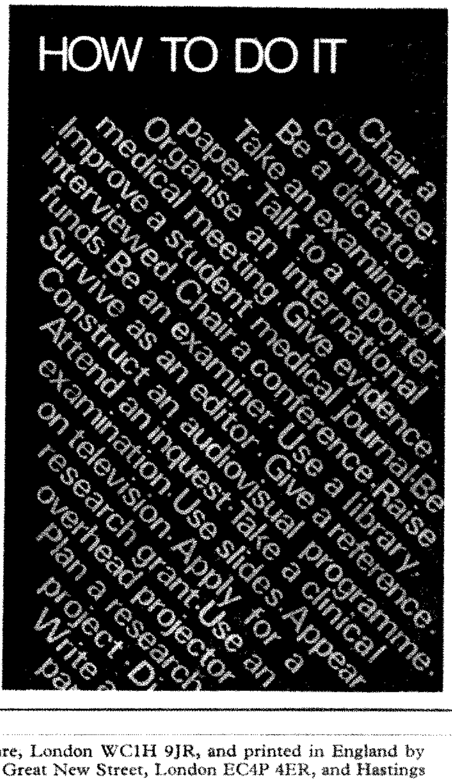
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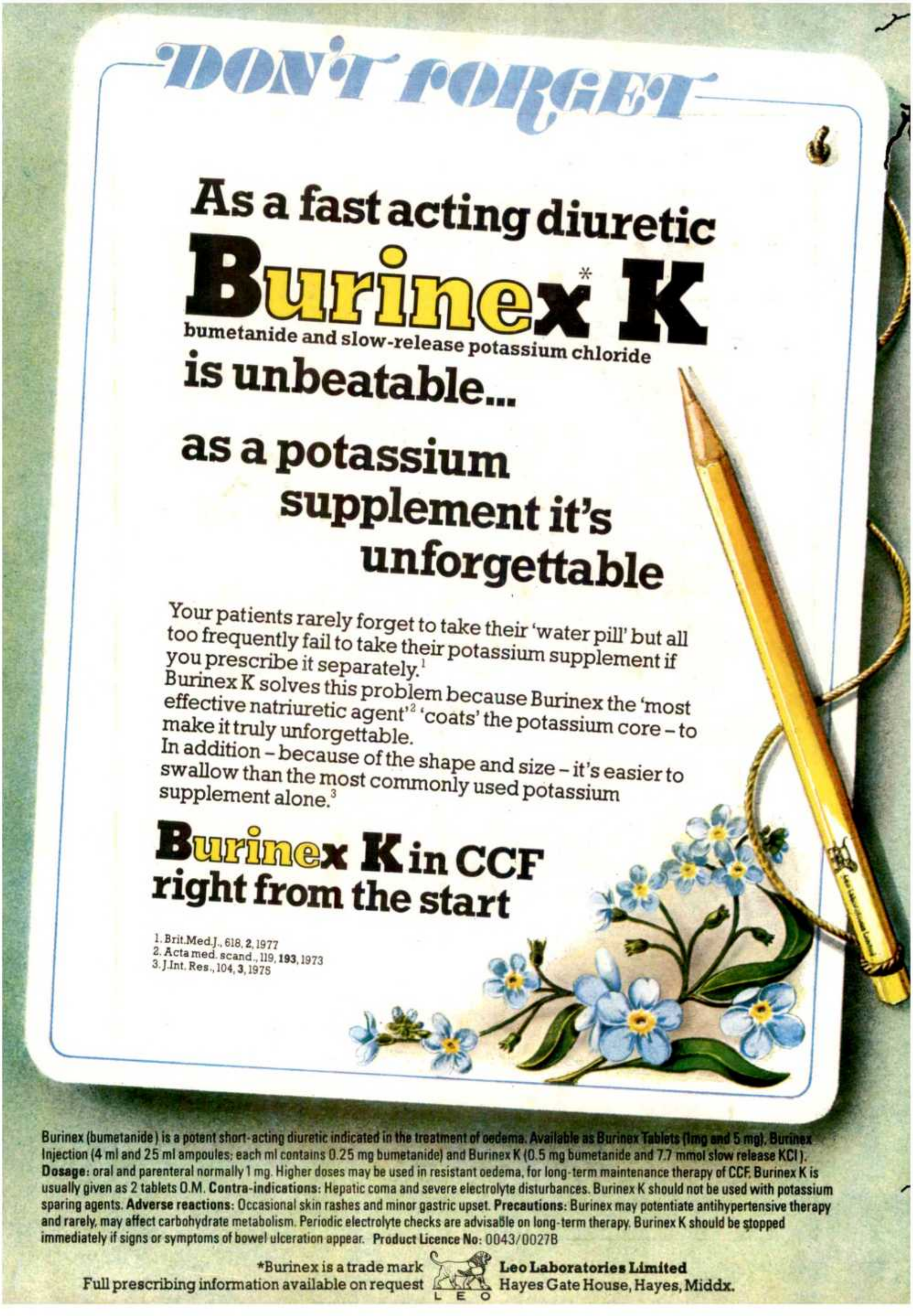

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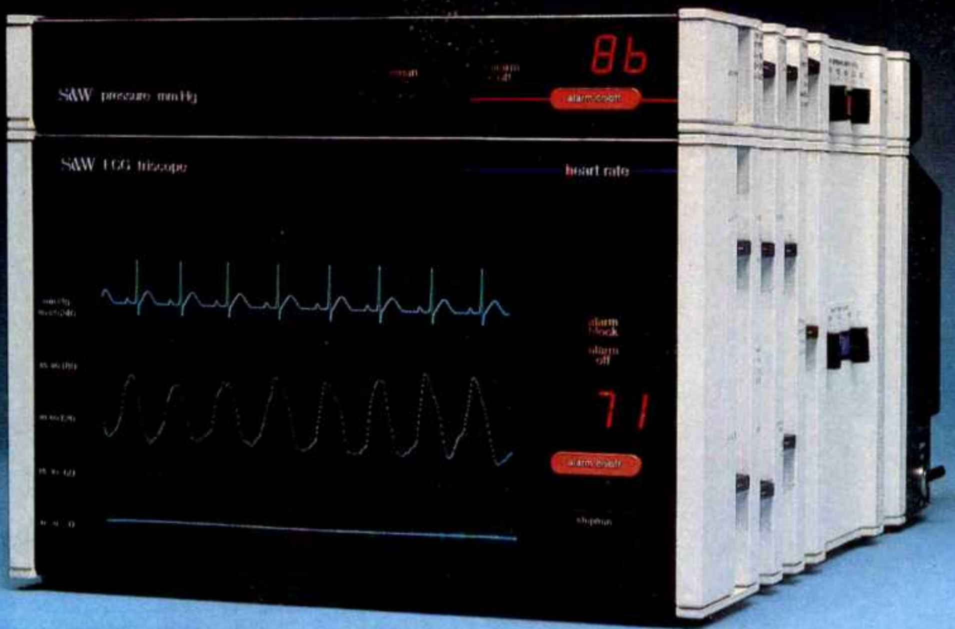

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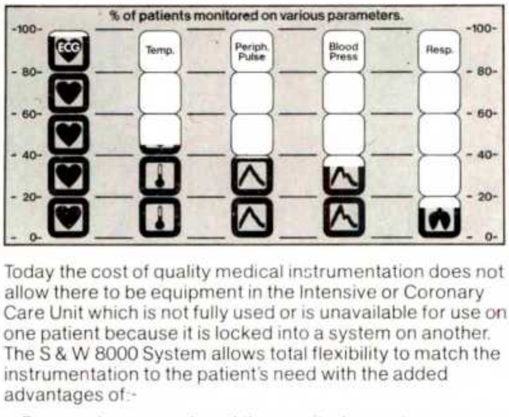

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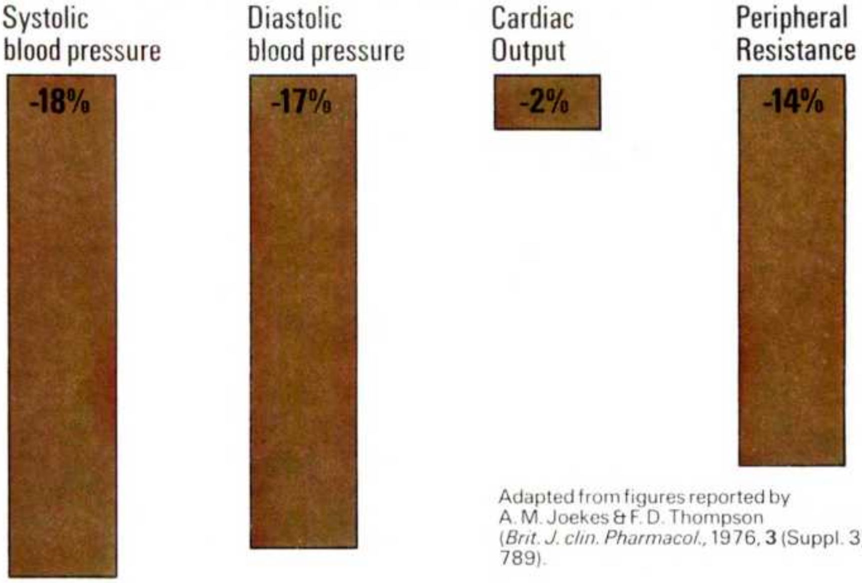

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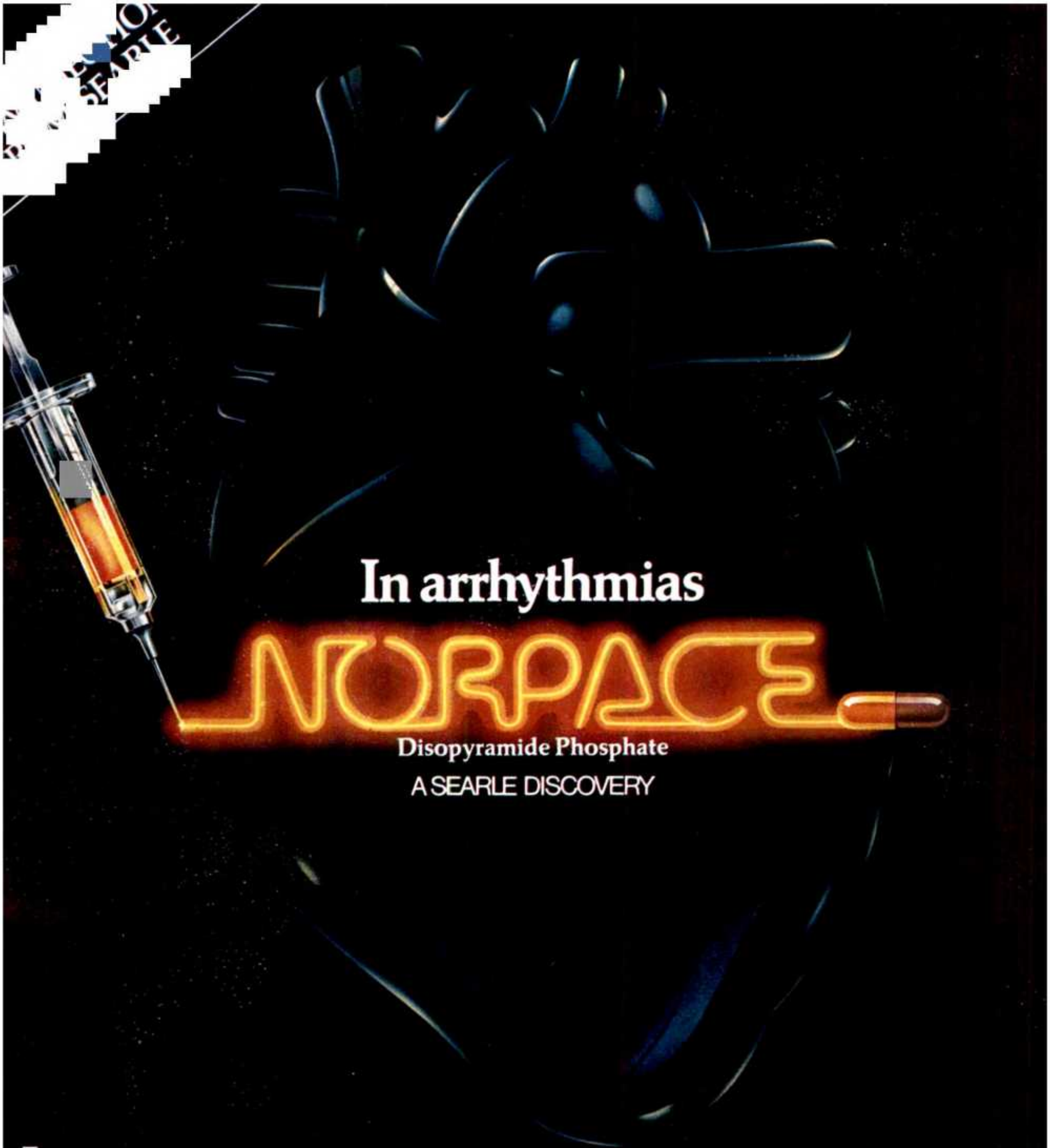

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2	USA Inter-Society Commission for Heart Disease Resources 1970. 'Primary prevention of atherosclerotic disease'.	✓
3	New Zealand Heart Foundation 1971. 'Coronary heart disease'.	✓
4	New Zealand Royal Society 1971. 'Coronary heart disease'.	
5	American Health Foundation 1972. 'Diet and coronary heart disease'.	✓
6	American Medical Association Council on Foods and Nutrition 1972. 'Diet and coronary heart disease'.	✓
7	American Heart Association Committee on Nutrition 1973. 'Estimating the risk of coronary heart disease'.	✓
8	International Society of Cardiology 1973. 'Myocardial infarction. How to prevent. How to rehabilitate'.	✓
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11 Australian National Heart Foundation 1974. 'Dietary fat and coronary heart disease.'	✓	**16** Norwegian Ministry of Agriculture 1976. 'Nutrition and food policy.'	✓
2 United Kingdom D.H.S.S. (C.O.M.A.) 1974. 'Diet and coronary heart disease.'		**17** United Kingdom Royal College of Physicians and the British Cardiac Society 1976. 'Prevention of coronary heart disease.'	✓
3 Australian Academy of Science 1975. 'Report of a working group on diet and coronary heart disease.'	✓	**18** F.A.O./W.H.O. Expert Consultation 1977. 'Dietary fats and oils in human nutrition.'	✓
4 Germany (F.R.) Federal Health Report 1975. 'Edible fats and circulatory disorders.'	✓	**19** US Select Committee on Nutrition and Human Needs 1977. 'Dietary goals for the United States.'	✓
5 Canada Health and Welfare 1976. 'Diet and cardiovascular disease.'	✓	**20** European Society of Cardiology 1978. 'Preventing coronary heart disease.'	✓

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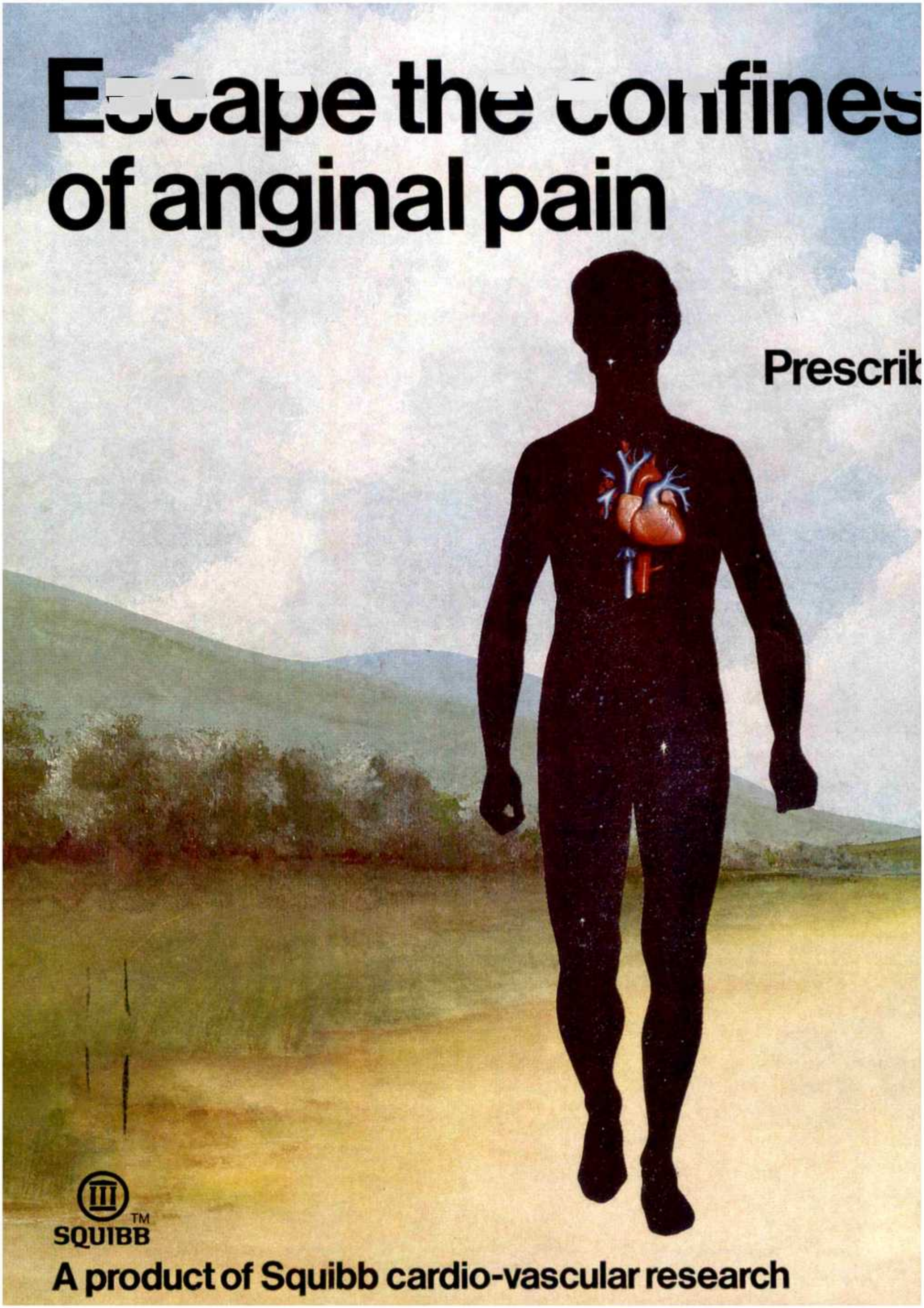

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Br Heart J 1980; **43:** 369–75

Use of first-pass radionuclide ventriculography in assessment of wall motion abnormalities induced by incremental atrial pacing in patients with coronary artery disease

DAVID STONE*, DUNCAN DYMOND, A T ELLIOTT, K E BRITTON, R A J SPURRELL, S O BANIM

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SUMMARY In order to show that stress-induced changes in ventricular function can be determined by radionuclide techniques, 13 patients with coronary artery disease were paced to angina. Changes in ejection fraction and regional wall motion were measured from contrast angiograms and first-pass nuclear angiograms performed using a multicrystal gamma camera. A count-volume method applied to the nuclear technique demonstrated a significant fall in ejection fraction on pacing. The area-length method was also applied to both techniques and a significant fall in ejection fraction was induced by pacing in both contrast and nuclear angiograms. There was a good correlation between ejection fraction on pacing derived from contrast and count-volume nuclear angiograms. Those patients with greater falls in ejection fraction were identified by both techniques. Changes in regional wall motion were assessed by a hemiaxial method. All six anterior and all four inferior pacing-induced zones of hypokinesis identified on contrast angiography were demonstrated by the nuclear technique. Of three apical regions of pacing-induced hypokinesis seen on contrast angiography one was shown by the nuclear method. All 11 zones of pacing-induced hypokinesis seen on nuclear angiography were in regions supplied by significantly stenosed coronary vessels.

Nuclear angiography is able to demonstrate changes in global and regional wall motion induced by ischaemia.

The non-invasive nature of radionuclide techniques allows them to play an important role in the assessment of ventricular function during stress. Before extending these methods to the dynamic exercise test, it is important to demonstrate that stress-induced changes in ventricular contraction seen on contrast angiograms could also be identified by radionuclide ventriculography.

Although left ventricular wall motion is known to be sensitive to ischaemia,[1] most angiographic studies of left ventricular function in patients with coronary artery disease have been performed at rest. Rickards *et al.*[2] have shown that ventriculograms performed under conditions of circulatory stress may demonstrate regional contraction abnormalities not seen in the resting state. In view of the fact that first-pass radionuclide ventriculography is capable of identifying localised wall motion abnormalities proven by contrast angiography,[3 4] a study was undertaken to investigate the usefulness of the technique in the detection of stress-induced changes in ventricular function. Since Sowton *et al.*[5] first described incremental atrial pacing as a method of inducing ischaemia, pacing has frequently been used for the assessment of ventricular function during pain.[6–9]

In this study we have investigated left ventricular function using both radionuclide and contrast angiography, at rest and at pacing-induced angina.

Patients and methods

The study group consisted of 12 male and one female patients aged between 37 and 62 years. All

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*Supported by a grant from Bayer (UK).

Received for publication 5 September 1979

were undergoing cardiac catheterisation for stable angina pectoris. Beta-blocking drugs were withdrawn 48 hours before the investigation and all patients received a premedication of 15 mg oral diazepam two hours before the procedure. Informed consent was obtained in every case.

CONTRAST ANGIOGRAPHY

Left heart catheterisation was carried out via a right brachial arteriotomy. A pacing catheter was passed into the right atrium via an antecubital vein. A resting left ventriculogram was performed in the 30° right anterior oblique projection with 20 to 30 ml of contrast medium. After three minutes, right atrial pacing was started at a rate of 100 beats per minute, increasing by 10 beats per minute every two minutes until the patient developed angina. When the pain had increased to moderate severity and persisted for one minute atrial pacing was discontinued and a second left ventriculogram performed at switch off using the same projection as at rest. Coronary arteriography was then carried out using the Sones technique.

RADIONUCLIDE ANGIOGRAPHY

Immediately after cardiac catheterisation the patient was transferred to the nuclear angiography laboratory and positioned under the detector of the multicrystal gamma camera (Baird-Atomic, System 77), in the right anterior oblique projection. After 30 minutes had elapsed from the end of coronary angiography, right atrial pacing to pain was restarted following the same procedure as above. At switch-off a 10 millicurie (mCi) bolus of technetium-99^m as pertechnetate was injected into the right atrium through the pacing catheter, with a rapid saline flush. Counting was carried out for 50 seconds at a framing rate of 20 per second. Data were collected on to disc and stored on magnetic tape, correction having been made for the dead-time of the instrument and flood-field non-uniformity. Twenty minutes later a static background frame of residual intracardiac radioactivity was counted with the patient in the same position as previously. This frame was then stored on disc. Immediately afterwards a 15 mCi bolus was injected and the resting study performed. Before storage on magnetic tape, this was corrected for background activity as well as for dead time and non-uniformity.

Data analysis

CONTRAST ANGIOGRAPHY

From the cine angiogram, end-systolic and end-diastolic frames were visually selected, ignoring ectopic and post-ectopic beats. Using the catheter position as a guide, the perimeters were traced and superimposed. The aortic valve plane was also delineated. The areas and long axes of the ventricles were measured using a computerised pressure-pad technique as previously described.[4] Ventricular volumes at end-systole and end-diastole were calculated by the area-length method modified for the right anterior oblique,[10] and ejection fraction derived. Wall motion abnormalities were quantified by a hemiaxial method similar to that of Dwyer,[11] and Leighton *et al.*[12] The long axis of the ventricle at end-diastole was trisected and two points obtained one-third and two-thirds of the distance along it from the aortic plane to the apex. Perpendiculars were drawn from these points to the ventricular perimeters in systole and diastole. Thus, five hemiaxes were generated, as shown in Fig. 1, there being two anterior, two inferior, and one apical hemiaxis. The percentage shortening of each hemiaxis was calculated using the formula:

$$\frac{\text{shortening of hemiaxis}}{\text{end-diastolic length of hemiaxis}}$$

A shortening of less than 25 per cent was defined as hypokinesis[3] and absence of inward wall motion as akinesis. All contrast angiograms, at rest and at pacing-induced angina, were analysed by this method.

RADIONUCLIDE ANGIOGRAPHY

After transferring the data from tape to disc, serial frames of each radionuclide study were summated over intervals of 1·5 seconds and the left ventricular phase identified. A region of interest was selected over the left ventricle using a magnetic pen and a grid array representing the 294 crystals of the detector. A time-activity curve from this region

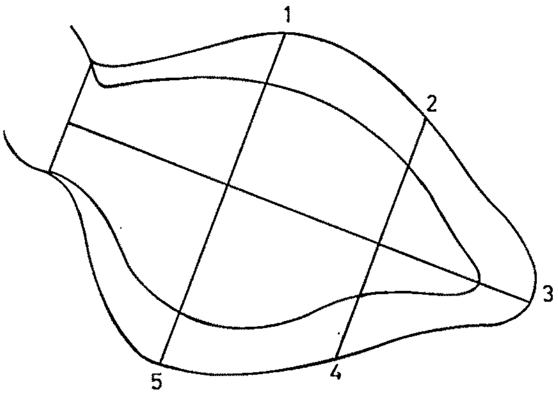


Fig. 1 *Hemiaxial model for wall motion analysis.*

was generated. A background frame was selected from the pulmonary phase and correction was automatically made spatially and temporally for the exponential decay of lung activity during all further data processing. The peaks and troughs of the laevo-phase, which represent end-diastolic and end-systolic counts, respectively, of individual cardiac cycles, were used to derive ejection fraction (count-volume method) and a representative cardiac cycle as previously described.[4] From this representative cardiac cycle end-systolic, end-diastolic, and stroke volume images were obtained. End-systolic and end-diastolic perimeters were generated from these images using an edge enhancement technique whereby the band of counts from 25 to 30 per cent of the maximal count in any one cell (N max) was isolated, and returned to normal in each study to the image with the lower N max. These perimeters were then superimposed in each case so that wall motion could be assessed. The area-length formula was used to calculate ventricular volumes from the perimeters, and thus a geometric ejection fraction was obtained. Wall motion abnormalities were assessed by means of the same hemiaxial method as for contrast angiograms, both at rest and at pacing-induced angina. Normal values for shortening of each hemiaxis were obtained from the radionuclide angiograms of 22 patients with no evidence of cardiac disease. The means and the ranges of shortening for each hemiaxis are shown in the Table. Hypokinesis of a hemiaxis was objectively defined as a percentage shortening of less than two standard deviations below the mean percentage shortening of that axis in normals. Akinesis was defined as for contrast angiograms.

CORONARY ARTERIOGRAMS

Coronary artery stenoses were regarded as significant if they were greater than 50 per cent of the luminal diameter.

Table *Normal values for hemiaxial model, based on 22 normal patients*

	Hemiaxis	*Normal range of shortening (mean ± 2 SD)*
Anterior	1	52·7 ±32·0
	2	81·7 ±31·2
Apical	3	83·0 ±36·5
Inferior	4	81·1 ±36·0
	5	37·2 ±37·6

Results

CORONARY ANGIOGRAPHY

Thirteen patients were studied. Six patients had triple vessel disease, five had double vessel disease, and two single vessel disease. Two of the patients had a significant left main stem stenosis.

EJECTION FRACTION

Fig. 2 shows the relation between the resting nuclear count-volume ejection fraction and the geometric ejection fraction derived from the contrast angiograms. Though there is a significant correlation ($r = 0·636$, $p < 0·05$), there was excessive scatter in the higher ejection fraction range. The method distinguished those patients with low ejection fraction. On pacing, the levels of ejection fraction obtained by the two methods are shown in Fig. 3. There is a better correlation ($r = 0·801$, $p < 0·001$)

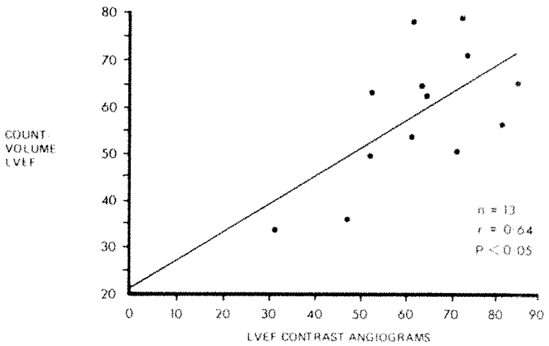


Fig. 2 *Relation between resting ejection fractions derived from contrast angiograms and count-volume nuclear angiograms.*

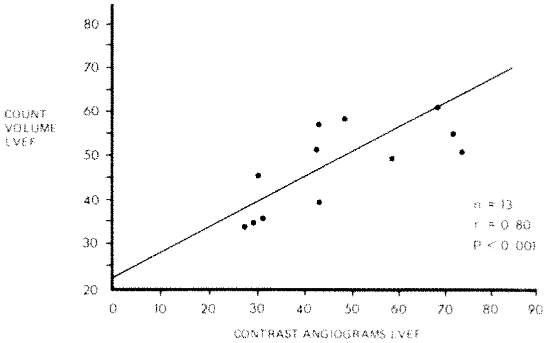


Fig. 3 *Pacing count volume nuclear angiogram ejection fraction versus pacing contrast angiogram ejection fraction.*

and this is consistent with the lower values obtained during angina by both techniques.

The change in ejection fraction caused by pacing to angina was calculated by contrast angiography and both nuclear methods (count-volume and area-length). Mean ejection fraction fell significantly for contrast angiograms from 62·6 to 40·3 ($p<0·05$). Geometric ejection fraction for nuclear angiograms fell from a mean of 71 to 55·1 ($p<0·02$) and mean count volume ejection fraction from 59·3 to 51·15 ($p<0·05$). Thus there was a significant fall in ejection fraction on pacing as judged by all three methods of analysis.

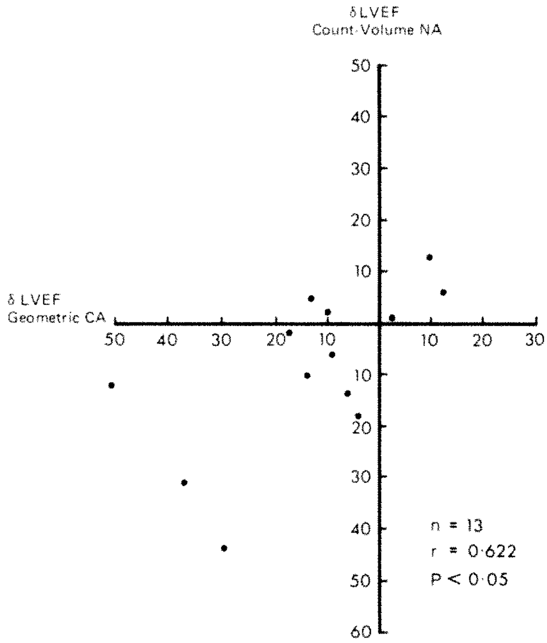


Fig. 4 *Change in ejection fraction induced by pacing. Correlation between count volume nuclear angiography and contrast angiography.*

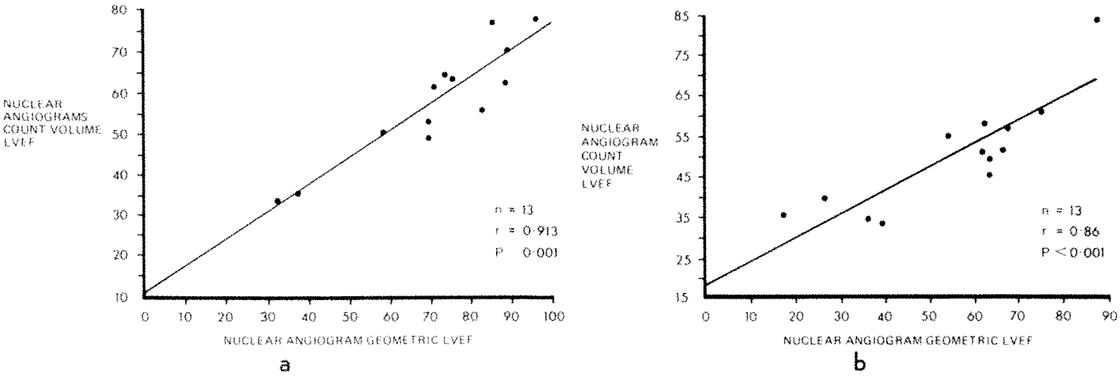
Fig. 4 shows the relation between the change in radionuclide ejection fraction assessed by the count volume and geometric contrast methods. There is a significant correlation between the two ($r=0·622$, $p<0·05$) and those patients with the larger falls in ejection fraction are identified by both methods.

There is a close relation between the area-length and count-volume methods which were applied to nuclear angiograms (Fig. 5a and 5b). There is a highly significant correlation at rest ($r=0·913$, $p<0·001$) and on pacing ($r=0·859$, $p<0·001$). Thus there was good evidence that either method may be applied to ejection fraction calculations and also that the perimeters used for the area-length method are valid.

Regional wall motion

All six pacing-induced anterior hypokinetic zones demonstrated by contrast angiography were identified by the nuclear technique also. Similarly, four of four inferior zones of pacing-induced hypokinesis assessed by contrast angiography were seen on nuclear angiography. One of three apical zones was demonstrated. Thus, of 13 zones of wall motion abnormality unmasked by pacing and shown by contrast angiography, 11 were seen by objective analysis of nuclear angiograms. The two cases which had apical abnormalities during pacing stress on contrast but not nuclear angiography had anterior hypokinetic segments demonstrated by the isotope technique.

The 11 zones of pacing-induced wall motion abnormality were seen in regions supplied by



a

b

Fig. 5 (a) *Rest and* (b) *pacing correlations between ejection fractions derived from the count volume and geometric nuclear methods of analysis.*

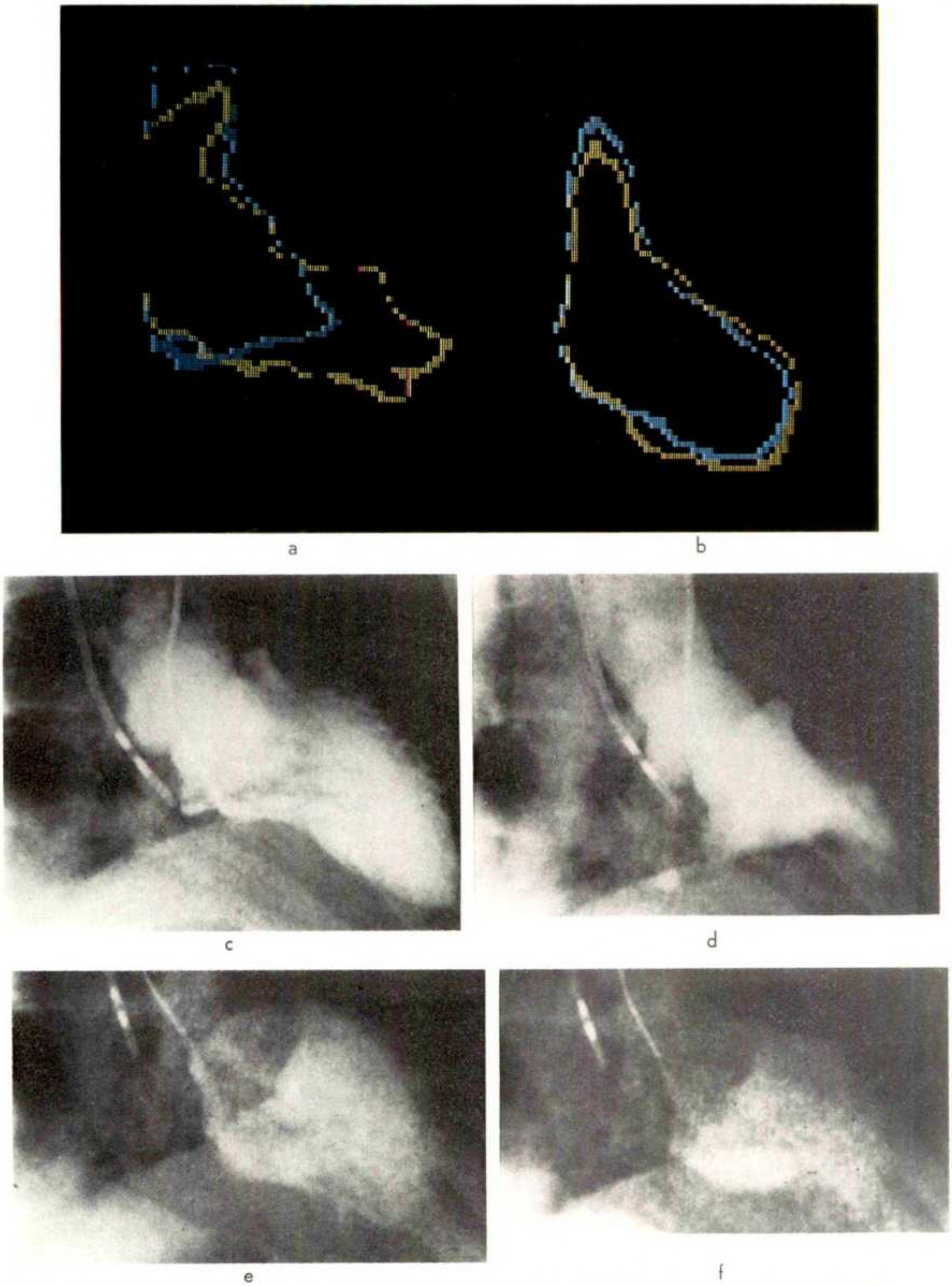


Fig. 6 *Change in ventricular contraction induced by pacing to angina.* (a) *Rest nuclear angiogram end-diastolic and end-systolic perimeters;* (b) *paced nuclear angiogram end-diastolic and end-systolic perimeters;* (c) *rest contrast angiogram end-diastole;* (d) *rest contrast angiogram end-systole;* (e) *paced contrast angiogram end-diastole;* (f) *paced contrast angiogram end-systole.*

significantly stenosed coronary arteries. Seven akinetic segments seen on the contrast angiograms were shown to be abnormal by the nuclear method. Three were inferior in location, two anterior, and two apical. All eight patients who developed pacing-induced abnormalities seen in the contrast study also had zones of hypokinesis unmasked by pacing during the nuclear study. Fig. 6 shows the change in ventricular contraction caused by pacing to angina in one of the patients. In both contrast and nuclear angiograms there is a distinct fall in ejection fraction on pacing, and generalised hypokinesia develops when assessed by both methods.

Discussion

First-pass radionuclide ventriculography is an accepted technique for the assessment of ejection fraction at rest[3 4 13] and has been correlated with contrast angiography. Dymond *et al.*[14] have also reported its use in the assessment of regional dysfunction caused by left ventricular aneurysms both at rest and on moderate exercise.

The major alternative to the first-pass technique in radionuclide ventriculography is that of gated blood pool scanning. Though this method has been shown to be reliable for the assessment of ejection fraction[15–17] an important limitation is that imposed by overlapping of cardiac chambers.[17 18] For this reason, the projection usually used in gated studies is the left anterior oblique which is not ideal for assessing regional wall motion abnormalities of the left ventricle.[19] Another problem is the length of time needed to collect data during a gated procedure. This has been reported as one to two minutes by Borer *et al.*[16] and up to eight minutes by Folland *et al.*[17] Therefore, it is extremly difficult to collect data representing the precise situation at the time of stress end-point. Borer *et al.*,[16] using the gated technique, reported changes in ejection fraction and wall motion during exercise in patients with coronary disease, though there was no comparison with contrast angiography at angina in these patients and also no quantification of wall motion abnormalities.

This is the first report of an assessment of wall motion abnormalities induced by myocardial ischaemia in the right anterior oblique projection which also affords a direct comparison with a contrast method. Since Sowton *et al.*[5] first described its use, atrial pacing has remained a useful tool for the induction of myocardial ischaemia in a relatively controlled situation.[3 6–9 11] Dwyer,[11] and Rickards *et al.*[2] report the unmasking of wall motion abnormalities by pacing at the time of contrast angiography. Marshall *et al.*[13 20] have shown good agreement between successive studies with the first-pass technique and Bodenheimer *et al.*[3] also showed that the order in which the respective obliques were used in a biplane study did not affect the results obtained. Thus, there is no evidence that significant errors are introduced by the performance of sequential studies without intervention.

The hemiaxial method of wall motion analysis was developed by Leighton *et al.*[12] for contrast angiograms, though Dwyer[11] used a similar technique for an assessment of pacing-induced abnormalities. Bodenheimer *et al.*[3] used the method in their assessment of wall motion abnormalities by first-pass radionuclide angiography at rest and found a good correlation between contrast and nuclear angiography in the right anterior oblique projection.

A possible criticism of our method is that, unlike Leighton *et al.*[12] and Bodenheimer *et al.*,[3] no allowance is made for shift of long axis between end-systole and end-diastole, which might lead to errors in assessment of apical wall motion changes. In this study, the definition of normal wall motion is based on the results of 22 patients without heart disease who were studied at rest.

In addition, all changes are occurring in the same patient between rest and exercise and compared with contrast angiograms analysed in the same way. Leighton *et al.*,[12] who did allow for axis shift, noted the wide variation in apical wall motion and felt that akinesis was necessary before wall motion abnormalities of the apical region could be judged as significant.

Both methods of analysis showed the expected fall in ejection fraction on pacing to angina. The overestimation of ejection fraction by the nuclear techniques in the patients with higher ejection fraction may be the result of a tendency to underestimate end-systolic volumes when they are small and, therefore, contain less counts. Since edge detection is dependent on Poisson statistics, the error increases as the count diminishes. The radionuclide technique proved reliable in the identification of abnormally contracting segments. All patients who developed wall motion changes as detected by contrast angiography were identified by the nuclear technique. Only in the apical region were changes seen on contrast angiography but not by the first-pass study. In those two patients there were anterior regions of hypokinesis which developed on pacing identified by both techniques. Thus, the wide variation in apical wall motion seen on contrast angiography[12] is paralleled by the nuclear techniques, and stricter criteria should perhaps be applied to the assessment of wall motion abnormality in this region.

This study has shown that first-pass radionuclide angiography can demonstrate changes in wall motion induced by acute ischaemic stress. This suggests that the technique may be extended with confidence to the assessment of wall motion changes induced by other forms of stress, for example exercise. Any changes that occur may be assessed in terms of global or regional ventricular function and allow the effect of interventions such as surgery or drug treatment to be judged at times of stress as well as at rest. In combination with the other non-invasive techniques it may also be able to play an important part in the screening of patients with coronary disease.

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Br Heart J 1980; **43**: 376–81

Praecordial surface mapping after exercise in evaluation of propranolol for angina pectoris*

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SUMMARY The effect of propranolol on ST depression in the praecordial 16 lead electrocardiogram was observed in 52 patients before and after treatment, both at rest and after exercise. In a further 20 patients exercise tests repeated on separate days two months apart showed that the technique gave reproducible results. A variable relation between symptomatic relief and praecordial exercise-induced ST segment depression was noted. Use of a single fixed-position chest lead (V5) was shown to be less accurate. The relief of symptoms alone is probably an inadequate guide to the success of medical treatment, which should control not only angina but also the manifestations of ischaemia on the praecordial electrocardiogram.

A non-invasive, objective means of assessing the effects of medical treatment would be invaluable for the management of patients with ischaemic heart disease, providing an important adjunct to symptomatic relief in determining the adequacy of treatment. Though exercise testing and measurements of exercise tolerance have proved useful, the subjective aspects involved in training and in pain assessment limit the usefulness of these techniques.[1] Few will deny the value of beta-blockade in controlling angina yet studies reporting the effects of propranolol on exercise-induced ST segment depression have been conflicting.[2–4] This must, in part, be related to the lack of quantitative data when measurements of the depth of ST depression are made at only one or, at best, six praecordial sites. The introduction of praecordial surface mapping after exercise adds an extra dimension to the standard lead systems since both the area and severity of ST segment changes that are projected on to the front of the chest can be measured.[5] The present study was designed, therefore, to determine the effects of established long-term beta-blockade on the praecordial projection of ST segment changes and to illustrate the value of this non-invasive objective technique in evaluating drug treatment in each individual patient.

Methods

Fifty-two patients (38 men, 14 women) with frequent incapacitating angina pectoris were studied. All reported daily episodes of chest pain and all developed ST segment depression after exercise. The mean age was 57 years. Before starting medical treatment, a 16 point praecordial electrocardiogram was recorded before and after exercise using a direct-writing ink jet Mingograf (Elema Schonander) recording on four channels simultaneously.[6] The 16 electrodes were connected to the electrocardiograph using a four-way switch. All patients developed chest pain during the exercise test, and this was used as the indication to stop the test.

The 16 unipolar electrodes were evenly distributed over the left hemi-thorax and connected to a central Wilson terminal. One of the positions corresponded exactly to V5 and was selected to act as the single chest lead for comparison purposes. Graded maximal exercise tests were performed using a bicycle ergometer.[7] Recordings were made before and immediately after exercise and then at regular intervals for 10 minutes or until the electrocardiogram had returned to the pre-exercise resting state. The connection of a patient took 10 to 15 minutes, and each 16 lead praecordial map about 10 seconds to record. The workload achieved by each patient was noted.

After the initial test, patients received treatment

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* This work was supported by a grant from the British Heart Foundation.

Received for publication 31 May 1979

as outpatients and were seen at least every two weeks. Propranolol was started at a dose of 10 mg three times daily and increased according to patient tolerance, symptomatic relief, and serial heart rate and blood pressure recordings. The mean final dose used was 300 mg daily in divided doses (range 120 to 480 mg) and compliance with therapy was assessed by questioning and by noting an adequate bradycardia at rest. When the optimal dose of propranolol in terms of symptomatic relief, heart rate response (less than 65/min), and drug tolerance had been achieved for each patient for at least two weeks, the praecordial electrocardiogram was repeated before and after exercise using the same procedure and workload as at the first test. Patients not suitable for treatment with propranolol, or unable to tolerate the drug, or considered not to be taking it properly were excluded from the study before the second test and are not part of these data.

A further 20 patients receiving no drug treatment were studied to determine the reproducibility of the praecordial area and severity of the ST segment depression. Exercise tests using the above procedure were repeated on separate days two months apart and the praecordial electrocardiogram was recorded before and after exercise. The same workload was used in both tests.

The criteria of the Scandinavian Committee on ECG Classification[8] were used to interpret the electrocardiograms. ST segment changes were read with reference to the PQ segment and depression was considered to be present if there was 1 mm or more of shift lasting for 0·08 second or longer. Contour maps of the area of ST segment change were drawn[9]; the total area being defined as the number of praecordial positions showing a significant ST segment alteration, and severity of ΣST as the total ST segment shift in millimetres for all the 16 positions.

Results

The mean resting and peak exercise heart rates (±1 standard deviation) were, respectively, 74±8 and 138±14 beats a minute before starting propranolol, and 56±5 and 92±6 beats a minute with treatment. The mean blood pressure before and after propranolol was 137/77 and 117/68 mmHg, respectively. All patients were able to achieve the same workload after treatment as at the beginning of the study

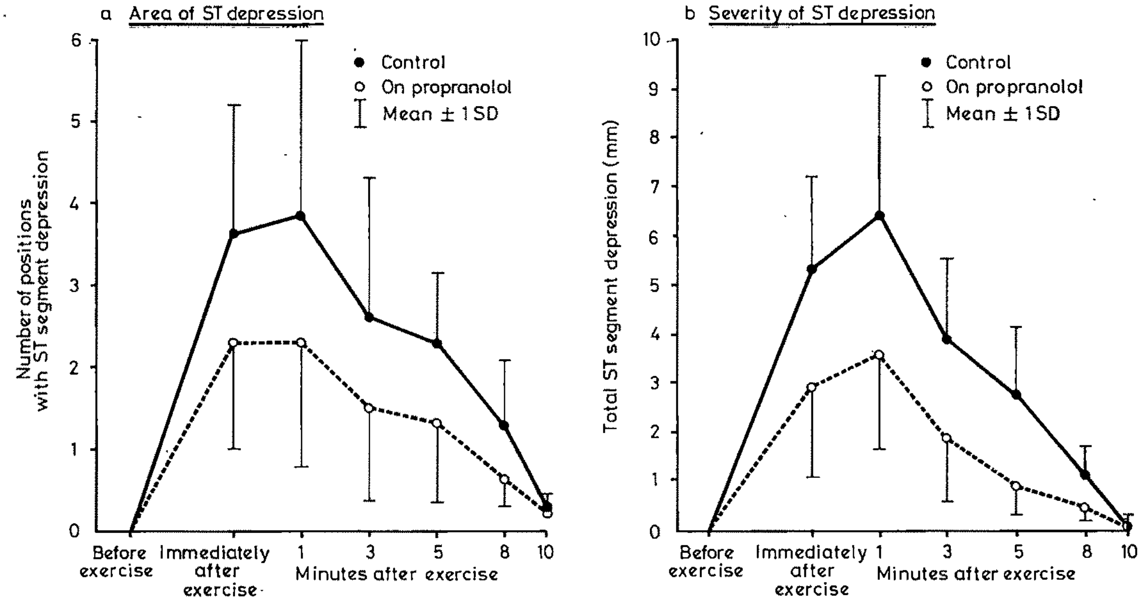

Fig. 1 (a) *The mean number of praecordial positions showing ST segment depression before and after exercise is shown before (control) and on treatment with propranolol in 52 patients. There were significantly fewer praecordial positions with exercise-induced ST segment depression during treatment with propranolol.* (b) *The total ST segment depression in millimetres for all 16 leads before and after exercise is shown before (control) and on treatment with propranolol in 52 patients. There was significantly less exercise-induced ST segment depression during treatment with propranolol. Mean and one standard deviation (SD) calculated; for clarity either the upper or lower extremity of the standard deviation is displayed.*

(mean 22 140 ± 9300 Watt s).

The mean time between the first and second exercise tests was eight ± three weeks.

Fig. 1a and 1b show the mean praecordial area and severity of ST segment depression recorded before and after exercise in the 52 patients before and after treatment with propranolol. Both the maximum area and maximum severity of exercise-induced ST segment depression were diminished after treatment with propranolol ($p<0{\cdot}01$). The wide individual variation is shown by the large standard deviation and the results have accordingly been divided into three groups.

GROUP 1: COMPLETE RESOLUTION OF EXERCISE-INDUCED PRAECORDIAL ST SEGMENT CHANGES WITH PROPRANOLOL (16 PATIENTS)

All these patients were free from pain on exercise when on propranolol. Nine had become free from symptoms at any time and seven now had chest pain infrequently. The single chest lead (V5) inevitably also showed complete resolution of ST segment changes after treatment (mean ST segment depression beforehand 1·25 mm). Fig. 2 recorded from a 48-year-old man shows an example. Both contour maps were obtained one minute after exercise, before and after propranolol 240 mg daily. This patient had been free from symptoms for four weeks before the second test was performed. Though exercising to the same workload, he did not develop ST segment depression.

GROUP 2: IMPROVEMENT IN EXERCISE-INDUCED PRAECORDIAL ST SEGMENT CHANGES WITH PROPRANOLOL BUT NOT COMPLETE RESOLUTION (16 PATIENTS)

Ten of these 16 patients were free from pain on exercise when on propranolol. Five had become free from symptoms at any time, seven now had chest pain only occasionally, but four still had frequent episodes of angina. The single chest lead (V5) showed complete resolution of ST segment changes in eight patients (mean ST segment depression before and after treatment 1·7 and 1 mm, respectively). Fig. 3 shows the sequence of contour maps recorded from one of these eight patients. Note that at position V5 there were no ST segment changes after treatment with propranolol. This patient was one of those now free from symptoms and without angina on exercise.

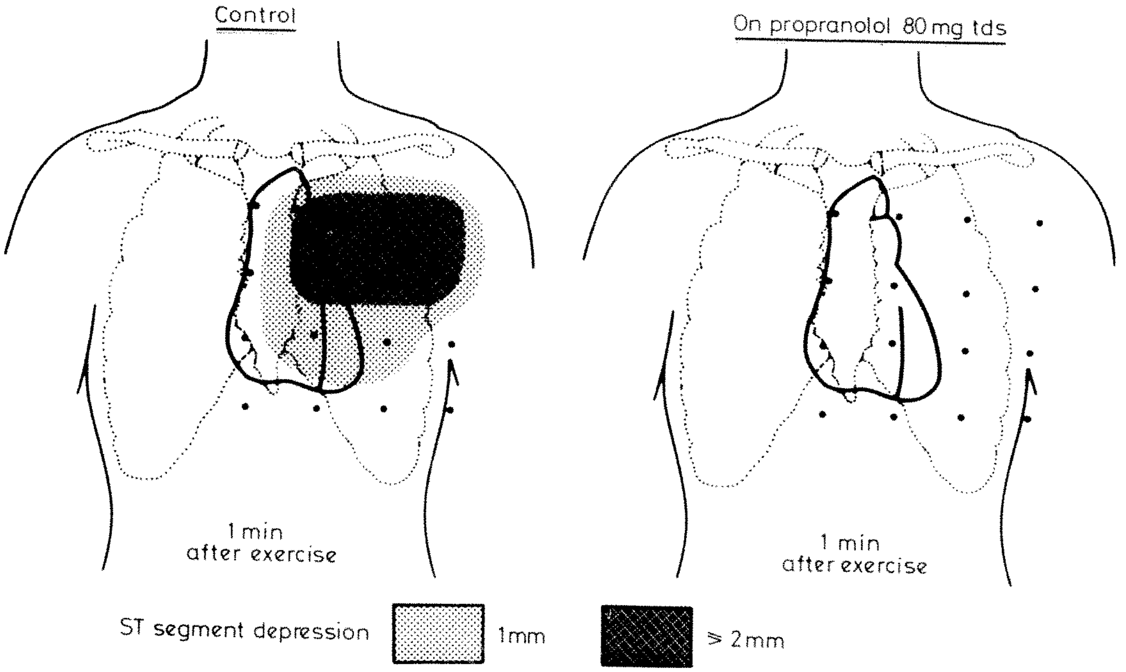

Fig. 2 *The maximum praecordial area of ST segment depression recorded after exercise (1 minute) is shown before treatment with propranolol (control). After propranolol no ST segment depression was recorded after exercise when the patient was exercised to the same work load.*

GROUP 3: NO CHANGE IN EXERCISE-INDUCED PRAECORDIAL ST SEGMENT CHANGES WITH PROPRANOLOL (20 PATIENTS)

Of these 20 patients, 12 were free from pain on exercise when on propranolol; one was now free from symptoms at any time, six had only occasional chest pain, and 13 still had frequent episodes of angina. The single chest lead showed complete resolution of ST segment changes in four patients (mean ST segment depression before and after treatment 1·7 and 1·2 mm, respectively). Fig. 4 shows the sequence of contour maps from a typical patient in this group. On propranolol this patient now had infrequent angina and was free of pain when exercised.

REPRODUCIBILITY

The mean praecordial area and severity of ST segment depression found at the first and second exercise tests in the 20 patients in whom reproducibility studies were performed are shown in Fig. 5a and 5b. There was no significant difference between the two tests before or at any time after exercise $(p > 0{\cdot}05)$.

Discussion

This study shows the value of being able to measure both the praecordial area and the severity of ST segment depression projected on to the front of the chest. Propranolol certainly reduces the frequency of angina and improves exercise tolerance but this does not necessarily indicate an improvement in the imbalance between myocardial oxygen supply and demand. Theoretically, the drug can increase coronary vascular resistance and this might make matters worse, though, in practice, such an effect is likely to be outweighed by the reduction in myocardial oxygen requirements.[10] Nevertheless, it is unclear whether relief of angina indicates total correction of the myocardial oxygen deficit or mere improvement in it.[11] Exercise, of course, exaggerates ischaemia, which, being frequently accompanied by ST depression, enables this point to be studied in so far as this electrocardiographic sign is specific. Though there is a variety of causes for this electrocardiographic sign, for example digitalis, hypertension, aortic stenosis, provided these are excluded, exercise-induced, downsloping or planar ST seg-

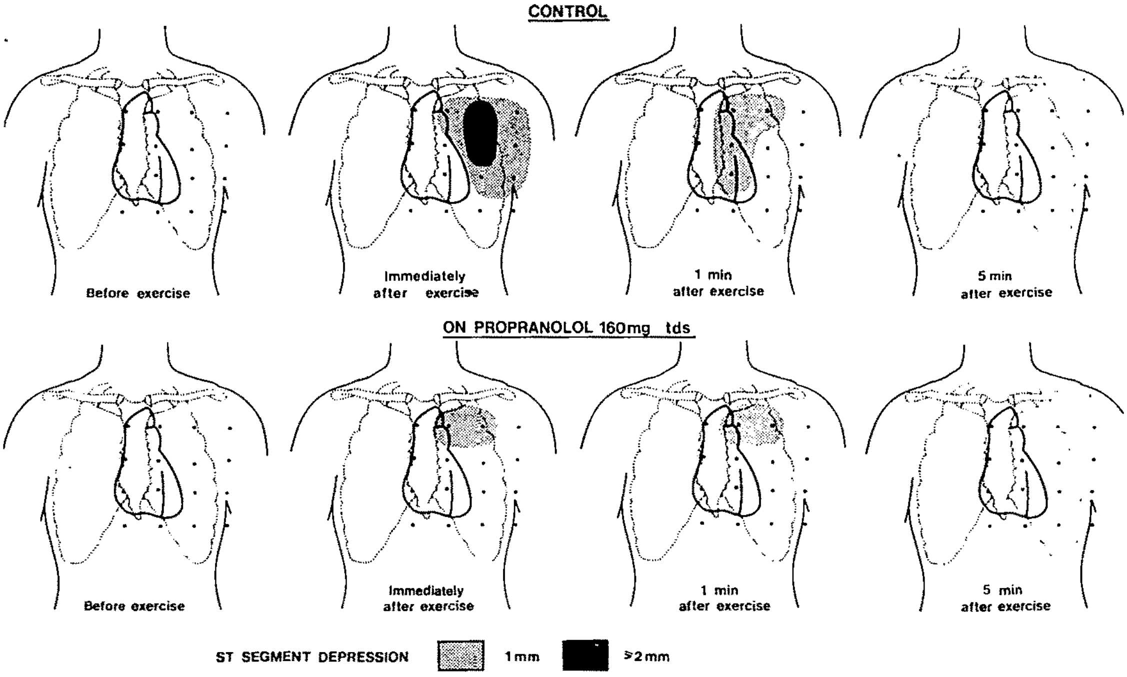

Fig. 3 *The sequence of contour maps obtained before (control) and on treatment with propranolol are shown. While on treatment with propranolol the praecordial area of ST segment depression was smaller and would not have been detected if only a single chest lead (V5) had been used.*

ment depression has been found to be specific for coronary artery disease.[5] Furthermore, experimental evidence has shown that it probably represents patchy myocardial ischaemia.[12] However, there are spatial and electrophysiological variables which prevent there being a simple quantitative relation between the extent of ischaemia and the area of abnormality on the electrocardiographic surface map,[13] and changes only have meaning if each patient acts as his own control.

This study has shown that the relief of angina is not necessarily accompanied by abolition of the electrocardiographic manifestations of ischaemia. ST segment changes after exercise increase as ischaemia increases; and the surface mapping technique can be used to make serial measurements in any individual patient, thus affording an objective measure of progress.

Furthermore, since angina pectoris and thereby ST segment depression can occur in a variety of circumstances, yet not necessarily always consistently, any technique to be used for serial measurements of ST segment changes must be reproducible and this has been shown for surface mapping, provided patients are exercised to the same workload under identical conditions on each occasion.

The discrepancies between previous reports on the effects of beta-blockers in angina become clear when the use of the single chest lead (V5) is compared with praecordial surface mapping in our patients. In 12 of them when on propranolol, reliance on V5 alone would have failed to identify exercise-induced ST segment depression that was present in other areas of the praecordium. Given the inconstant relation between the heart and the front of the chest with alterations in position, respiration, and heart rate, this is not surprising, and no single fixed position lead can be considered a reliable indicator of ST segment change.

The relations between symptomatic relief, exercise-induced chest pain, and the praecordial electrocardiographic signs of ischaemia after propranolol are of particular interest. The relief of symptoms did not necessarily run parallel with the effective control of exercise-induced ST changes, though an improvement in symptoms was never found in association with a deterioration in the

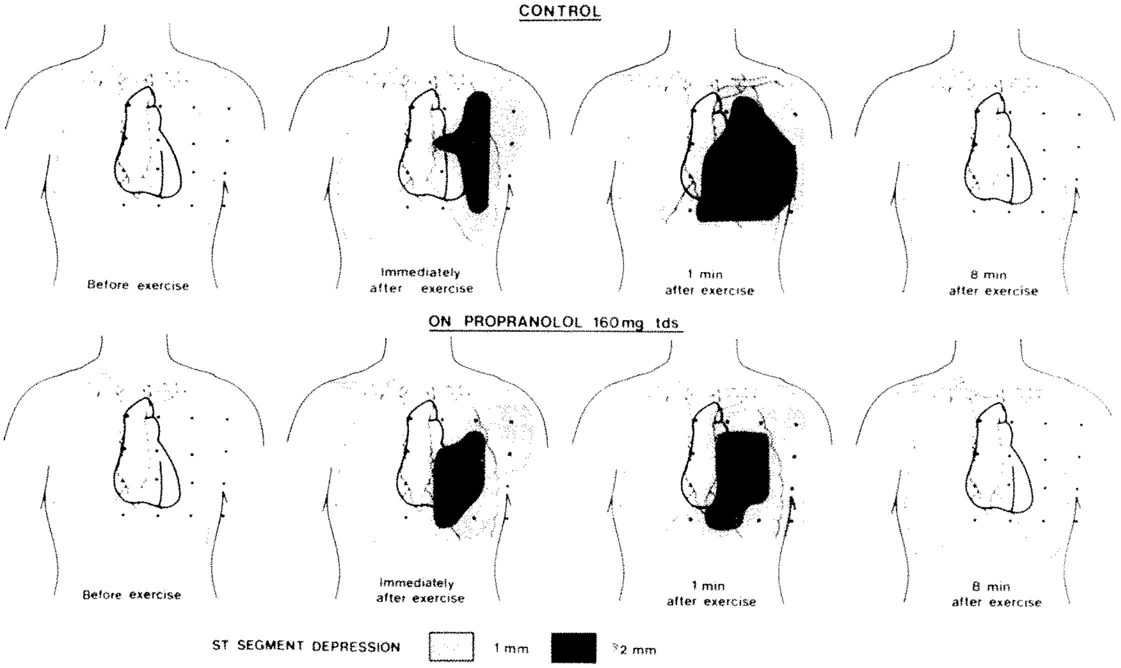

Fig. 4 *The sequence of contour maps obtained before (control) and on treatment with propranolol are shown in a patient in whom the praecordial area of ST segment change was little affected by the propranolol.*

electrocardiogram. A reduction in exercise-induced chest pain was a more reliable accompaniment to the relief of symptoms but correlated poorly with any improvement in ST segment depression. The significance of exercise-induced ST segment changes in the absence of pain in patients on propranolol is unclear and further work is necessary to show if there is any prognostic improvement when the electrocardiographic manifestations of myocardial ischaemia are controlled.

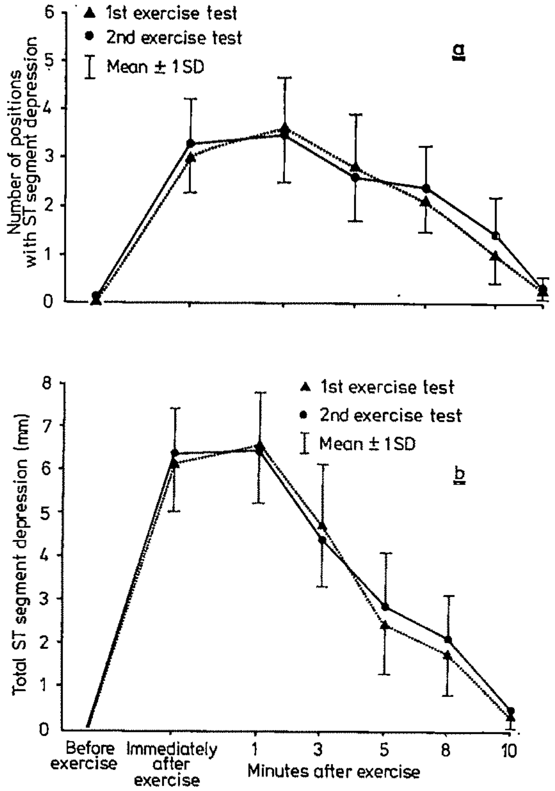

Fig. 5 *The mean number of praecordial positions showing ST segment depression (*a*) and the mean ST segment depression in millimetres for all 16 leads (*b*) is shown for each of the two exercise tests in the 20 patients in whom reproducibility studies were performed. Both the praecordial area and severity were similar before and at each time after exercise in both tests. Mean and standard deviations displayed as in Fig. 1.*

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Br Heart J 1980; **43**: 382–7

Left ventricular function in presence of small pericardial effusion
Echocardiographic study

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SUMMARY Using echocardiography, various indices of left ventricular function were studied in a group of 11 patients with small posterior pericardial effusion. The only index of left ventricular function that was abnormal in this group was maximum diastolic endocardial velocity (DEVM), a measure of left ventricular relaxation. When evaluated as a group, DEVM was significantly decreased in the presence of effusion as compared with the control group. This change in DEVM in the presence of small effusion, without any other associated changes in left ventricular function, suggests that the mechanism of impaired left ventricular relaxation is a change in compliance of the pericardium. In large effusions, left ventricular relaxation abnormalities are associated with changes in left ventricular dimensions, and impaired relaxation may also be the result of shift in intracardiac structures.

Reflected ultrasound has become the primary diagnostic tool for pericardial effusion since the pioneering work of Edler[1] and Feigenbaum.[2] Many studies have evaluated its sensitivity and specificity in the diagnosis of pericardial effusion.[2–4] Others have used echocardiograms to quantify the size of effusions.[5] Recent reports have used various echocardiographic measurements of the mitral valve and left ventricle to explain some of the physical signs associated with pericardial effusion and cardiac tamponade.[6–8]

There have been few studies of left ventricular function in pericardial effusion. The reason may be that with large pericardial effusion, the whole heart oscillates within the pericardial sac, resulting in an exaggerated motion of the posterior wall. Conventional measurements of left ventricular function are, therefore, not applicable.[9–11] Because of this, we decided to study various indices of left ventricular function in a group of patients with small-to-moderate posterior pericardial effusion with no anterior effusion. The purpose of this study was to determine which of these indices is impaired in a small pericardial effusion and to consider the mechanism of this impairment.

Received for publication 20 July 1979

Methods

Echocardiograms of patients with posterior pericardial effusions were selected from the files of the paediatric heart station of the Johns Hopkins Hospital. Patients with an anterior component to the effusion were excluded in order to minimise swinging of the heart. Each patient also had a control echocardiogram taken when no effusion was present. Thus, the indices measured in the presence of an effusion for each patient could be compared with his own control.

Eleven patients satisfied these criteria and ranged in age from 4 to 17 years, with a mean of 10 years. The causes of pericardial effusion were varied and included uraemia, neoplasm, collagen vascular disease, and post-pericardiotomy syndrome. Echocardiography was performed on a Smith Kline Ekosector I interfaced with a Honeywell Stripchart Visicorder. The ultrasound beam had a frequency of 3·5 or 2·25 MHz, with the former non-focused and the latter focused at 7·5 cm.

The indices measured on each echocardiogram were internal left ventricular systolic and diastolic diameter, maximum diastolic endocardial velocity (DEVM), maximum systolic endocardial velocity

(SEVM), anterior mitral leaflet excursion, and EF slope of anterior leaflet of mitral valve. Maximum diastolic endocardial velocity and systolic endocardial velocity were measured by drawing a tangent along the maximum systolic and diastolic motion of the posterior wall of the left ventricle. An example of such a measurement is shown in Fig. 1. Late diastolic endocardial excursion (LDEE) was determined as in Voelkel *et al.*[12] Measurements were made from the crystal artefact to the endocardium at the end of the rapid diastolic relaxation phase and at the beginning of systolic isotonic contraction in the next cardiac cycle: the difference between these two is the LDEE. Indices were measured by two independent observers; there was excellent concordance.

Results

The mean size of the posterior pericardial effusion for the selected patients was 1·5 cm, with a range of 0·8 to 4·1 cm. A sample for one patient is illustrated in Fig. 2. All measurements are reported as mean ± standard error. The results of the various indices are given in the Table.

(1) MAXIMUM DIASTOLIC ENDOCARDIAL VELOCITY (DEVM)

The DEVM for all 11 patients was significantly less in the presence of posterior pericardial effusion than their respective control values ($p < 0{\cdot}001$). When taken as a group, the average DEVM with effusion (102 ± 11 mm/s) was less than the average control value (145 ± 12 mm/s) ($p < 0{\cdot}02$) (Fig. 3).

(2) MAXIMUM SYSTOLIC ENDOCARDIAL VELOCITY (SEVM)

There was no significant correlation between the presence of pericardial effusion and the SEVM ($p > 0{\cdot}5$). The SEVM with effusion was 61 ± 4 mm/s, and without effusion it was 60 ± 4 mm/s (Fig. 4).

(3) LATE DIASTOLIC ENDOCARDIAL EXCURSION

There was no correlation between the LDEE and the presence (1·8 ± 0·5 mm) or absence of effusion (1·9 ± 0·4 mm) ($p > 0{\cdot}5$).

(4) LEFT VENTRICULAR DIMENSIONS

There was no significant correlation between the presence of small posterior pericardial effusion and left ventricular systolic or diastolic diameters ($p > 0{\cdot}5$). Only two of the 11 patients had significant decreases in both dimensions. Of these two, one had the largest effusion in this study (4·1 cm posterior). When this patient's effusion resolved, his systolic diameter increased from 4·2 to 5·4 cm and the diastolic diameter increased from 5·3 to 6·2 cm. The other patient had the second largest effusion (2·4 cm posterior) and had an increase in systolic and diastolic diameters when the effusion resolved. Systolic diameters increased from 2·1 to 3·5 cm and diastolic 3·4 to 3·8 cm, respectively.

(5) MITRAL VALVE INDICES

There was no significant difference in the EF slope

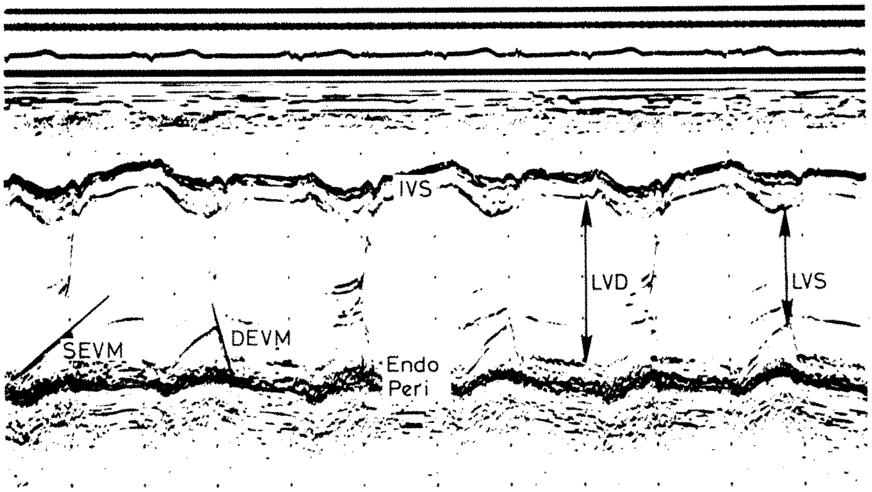


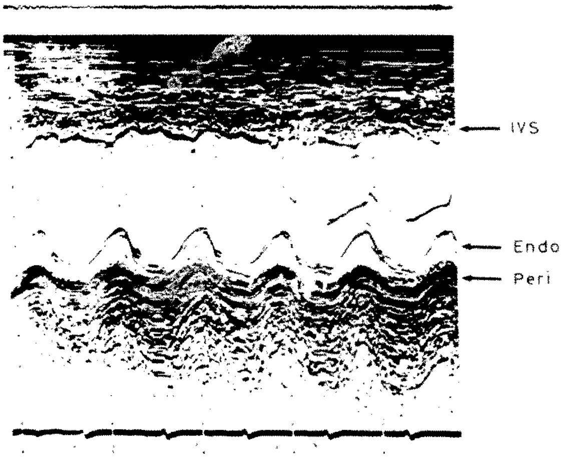
Fig. 1 *Normal echocardiogram. LVS, left ventricular systolic internal diameter; LVD, left ventricular diastolic internal diameter; Peri, pericardium; Endo, endocardium; DEVM, maximum diastolic endocardial velocity; SEVM, maximum systolic endocardial velocity; IVS, interventricular septum.*

of the anterior leaflet of the mitral valve in the presence of effusion (133 ± 12 mm/s) compared with controls (135 ± 14 mm/s) ($p > 0{\cdot}5$). Similarly, no significant difference in mitral valve excursion was observed (21 ± 1 mm both with and without effusion ($p > 0{\cdot}5$)).

Discussion

The effective ventricular filling pressure is the difference between the intraventricular and extraventricular pressures. Since the heart is invested in the pericardium, pericardial pressure is a major determinant of extraventricular pressure.

Without pericardial effusion



With pericardial effusion

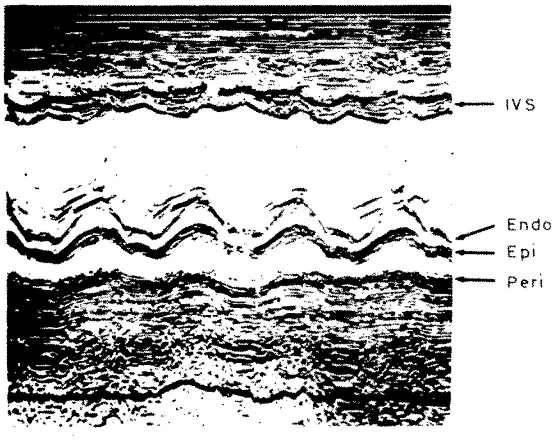


Fig. 2 *Echocardiogram for a patient with and without posterior pericardial effusion. IVS, interventricular septum; Endo, endocardium; Epi, epicardium; Peri, pericardium.*

The pericardial pressure is a function of intrapericardial volume and the rate at which this volume changes. If the change is acute, pericardial pressure-volume characteristics are non-linear, with the slope increasing as volume increases.[13] This, by definition, indicates that the pericardial compliance decreases with increasing volume and pressure. Because of the intimate association between the heart and the pericardium, a decrease in pericardial compliance will decrease the effective ventricular compliance.

Under normal circumstances, the pericardium imposes a slight restrictive force on ventricular filling. In the dog heart-lung preparation, when the pericardium is removed, this extraventricular restrictive force is removed, allowing venous pressure to drop without compromising ventricular filling or cardiac output.[14] In addition, hypervolaemic pericardiectimised dogs have a dilated left ventricle.[15]

In the dog, if pericardial pressure is increased by injecting saline or air into the pericardium, the effective ventricular filling pressure is decreased and cardiac output decreases.[13] If the pericardial pressure is increased enough to cause cardiac tamponade, the effective filling pressure is decreased to the point where there is a loss of early rapid left ventricular diastolic filling and severe restriction of cardiac output.

When cardiac tamponade occurs in humans, there are certain characteristic echocardiographic changes. Cyclic respiratory variations in mitral valve EF slope[6 8 16] and septal motion[7] have been suggested as explanations of pulsus paradoxus caused by decreased left ventricular filling. Large pericardial effusions that have not yet progressed to tamponade do not have these features,[8 16] though swing of the heart[9–11] and false positive appearances of mitral valve prolapse[16–18] have been noted by many observers.

In this study, we examined patients with effusions too small to cause cardiac tamponade and found a significant decrease in the maximum diastolic endocardial velocity when compared with controls. Because we restricted our patient population to those with no anterior component to their effusion, cardiac swing is minimised. This implies that the decreased DEVM is not merely a reflection of motion of the heart as a whole, but instead represents a slowed ventricular relaxation in early diastole. Swing of the heart observed in large effusions tends to accentuate indices of posterior wall motion. This was observed by Vignola *et al.*,[16] who measured an increase in the diastolic epicardial velocity in the presence of moderate to large

Table *Echocardiographic data*

Case no.	*Size of post. effusion (cm)*	*Diameter*		*SEVM (mm/s)*	*DEVM (mm/s)*	*Mitral excursion (cm)*	*LDEE (mm)*	*EF slope (mm/s)*
		LV systolic (cm)	*LV diastolic (cm)*					
1	1·8	3·0	4·3	69	92	2·2	3·0	186
	0	3·0	4·3	77	175	2·2	3·0	238
2	1·1	2·6	4·0	74	82	—	1·5	—
	0	2·1	3·4	68	160	—	1·0	—
3	1·1	2·1	3·5	47	46	1·8	—	84
	0	2·5	3·3	42	84	1·7	3·0	87
4	1·2	3·0	5·8	79	155	3·1	3·5	156
	0	3·2	4·9	73	168	2·3	3·5	124
5	1·3	3·8	6·0	80	117	2·0	0·0	188
	0	3·8	6·2	77	135	2·1	0·5	175
6	0·8	1·9	2·7	46	84	1·5	2·5	125
	0	2·0	2·8	45	119	1·5	2·5	104
7	2·4	2·1	3·4	65	157	1·5	1·0	123
	0	2·5	3·8	65	202	1·9	1·0	121
8	1·0	2·0	3·0	56	95	1·9	1·5	109
	0	2·3	4·0	53	138	2·1	2·5	126
9	4·1	4·2	5·3	54	107	2·3	0·0	156
	0	5·4	6·2	40	133	2·2	0·0	156
10	0·8	3·7	5·0	50	55	2·2	1·5	87
	0	3·3	4·5	52	89	2·0	2·5	109
11	0·9	3·1	5·0	43	134	2·5	4·0	113
	0	2·6	4·5	65	196	2·6	2·5	106

SEVM, maximum systolic endocardial velocity; DEVM, maximum diastolic endocardial velocity; LDEE, late diastolic endocardial excursion.

effusions. We measured endocardial rather than epicardial velocity, and excluded patients with cardiac swing, so our results cannot be compared with those of Vignola *et al.*[16]

DEVM has been used as a measure of ventricular relaxation.[19 20] The decrease in DEVM in the presence of pericardial effusion measured in this study suggests that the diastolic relaxation of the left ventricle is impaired. This impairment is probably the result of an increase in pericardial pressure and a decrease in pericardial compliance. We cannot exclude primary myocardial disease as the cause of the decrease in DEVM. This seems less likely because the echocardiographic variables traditionally employed to evaluate left ventricular function are not impaired. In addition, the increase in DEVM after resolution of the effusion argues against myocardial dysfunction. Our data corroborate the early dog studies of Isaacs *et al.*,[13] in which increased pericardial fluid decreased pericardial compliance and increased pericardial pressure, resulting in impaired ventricular relaxation. Since the primary functional defect appears to involve diastolic relaxation, it is not surprising that we found no change in the maximum systolic endocardial velocity.

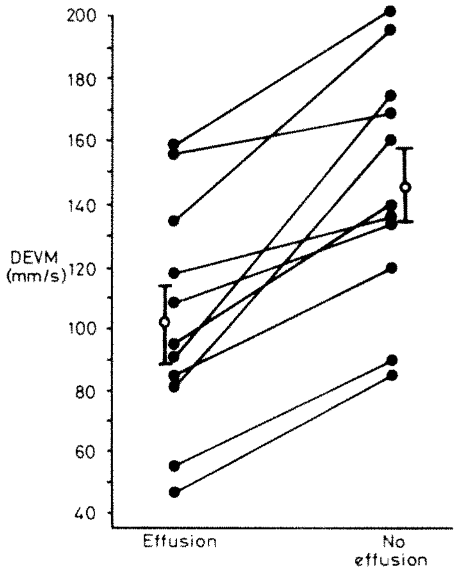


Fig. 3 *Maximum diastolic endocardial velocity (DEVM) for patients with and without posterior pericardial effusions.* ●*, data points;* ⫮ *, mean ± SE.*

The decrease in DEVM in the presence of effusion implies that the rate of early diastolic relaxation is impaired. However, a measure of the absolute amount of relaxation, the late diastolic endocardial excursion, is not affected by small effusions. If one thinks of the heart as being inside a balloon, the compliance of the balloon, representing the pericardium, will decrease as fluid is added. Though this will slow the rate of ventricular filling, the final ventricular volume and the LDEE will be the same. Our finding that left ventricular dimensions are not affected by small effusions supports this. Voelkel *et al.*[12] demonstrated a decrease in LDEE in patients with constrictive pericarditis. Here, the pericardium acts as a fixed barrier to late diastolic filling, as if the heart were in a rigid box. The primary defect is impaired posterior wall excursion rather than the rate of early diastolic relaxation.

A decreased EF slope of the anterior leaflet of the mitral valve has been used as a sign of decreased ventricular compliance.[21] We found no significant decrease in the mitral EF slope or in the mitral excursion in the presence of effusion. However, as noted above, only effusions large enough to cause tamponade cause cyclic changes in mitral valve behaviour related to respiration. It appears, therefore, that DEVM is a more sensitive measure of impaired ventricular relaxation secondary to pericardial effusion.

Left ventricular systolic and diastolic internal diameters have been shown to decrease with increased pericardial pressure.[22] However, in the presence of the small effusions observed in this study, we found no significant decrease. This apparent discrepancy is probably quantitative rather than qualitative since the pericardial pressures generated by the small effusions in our patients were probably not high enough to affect ventricular dimensions.

Both large and small pericardial effusions result in impaired left ventricular relaxation, but the mechanism appears to be different. In large effusions there are significant changes in systolic and diastolic dimensions of the left ventricle suggesting that the mechanism of impaired left ventricular relaxation may be the result of shift in intracardiac structures such as the interventricular septum. In small effusions, as is shown by the present study, DEVM, a measure of left ventricular relaxation, is significantly decreased without any associated changes in other left ventricular function indices. This strongly suggests that in small pericardial effusions, impaired left ventricular relaxation is secondary to decreased pericardial compliance and increased pericardial pressure.

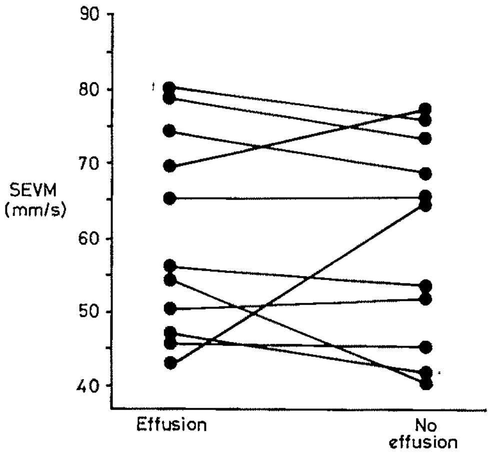


Fig. 4 *Maximum systolic endocardial velocity (SEVM) for patients with and without posterior pericardial effusions.* ●, *data points.*

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Br Heart J 1980; **43:** 388–92

Combined use of phenoxybenzamine and dopamine for low cardiac output syndrome in children at withdrawal from cardiopulmonary bypass

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SUMMARY The combined use of phenoxybenzamine and dopamine was applied in infants and children when it was difficult to come off cardiopulmonary bypass for low cardiac output. The rationale of this method is to prevent the alpha-adrenergic action of dopamine by phenoxybenzamine and to encourage the beta-adrenergic and direct specific action of dopamine. Dopamine was used in dosage of 10 to 30 μg/kg per min after the additional administration of a half of the initial dosage of phenoxybenzamine; this was infused by drip always in a dosage of 0·5 to 1·0 mg/kg during the first half of cardiopulmonary bypass.

It was possible to come off cardiopulmonary bypass with a stable haemodynamic state (mean arterial pressure more than 60 mmHg and total peripheral vascular resistance less than 2000 dynes s cm^{-5}) and a good urinary output.

Dopamine is a biochemical precursor of norepinephrine which increases myocardial contractile force by a beta-adrenergic action and produces mild vasoconstriction by an alpha-adrenergic action.[1] It also produces renal and mesenteric vasodilatation by a direct specific action, not antagonised by either alpha- or beta-adrenergic blocking agents.[2 3] This unique combination of properties provides a rational basis for the use of dopamine in the treatment of cardiogenic shock.

The combined use of dopamine and phenoxybenzamine, an alpha-adrenergic blocking agent,[4 5] was attempted in the treatment of low cardiac output syndrome in patients coming off cardiopulmonary bypass.

Subjects and methods

Studies were made on 27 patients (age range 8 months to 6 years and 8 months) with congenital heart disease, who underwent open-heart surgery at Meijyo Hospital from July 1977 to June 1978 (Table 1). The combined use of phenoxybenzamine and dopamine was attempted in nine patients where difficulty had occurred in attempting to come off cardiopulmonary bypass. The other 18 patients, in whom phenoxybenzamine only was used, were studied as controls (Table 2).

Cardiopulmonary bypass was accomplished with a small roller pump arranged for paediatric perfusion and a Temptrol oxygenator designed for infants. The haemodilution ratio was 35 to 45 per cent using the normothermic method and 20 to 35 per cent using the hypothermic method. The perfusion flow was checked and controlled every 15 minutes during cardiopulmonary bypass in order to maintain optimum perfusion.[6] It resulted in a perfusion index of 3·4 to 3·9 l/m² per min at 15 minutes of bypass at which time the haemoglobin concentration showed the minimum value. Total circulatory arrest within 30 minutes was applied when the oesophageal temperature was 20°C (Table 2). The practice of administration of phenoxybenzamine and dopamine is as follows. Phenoxybenzamine was infused by drip into an oxygenator at a dosage of 0·5 to 1·0 mg/kg within the first half of cardiopulmonary bypass in all cases of this series. Whenever dopamine was necessary in the cases in which it was difficult to come off cardiopulmonary bypass, dopamine 10 to 30 μg/kg per min was given after the additional administration of half the initial dose of phenoxybenzamine and was gradually reduced.

Arterial pressure (AP), central venous pressure (CVP), perfusion flow, urinary output, body temperature, electrocardiogram, and electroencephalogram were monitored continuously. Blood gas analysis, acid-base status, electrolyte balance,

Received for publication 2 July 1979

haemoglobin, and free haemoglobin values were measured at 15-minute intervals during cardiopulmonary bypass. The perfusion index (PI) and total peripheral vascular resistance (TPVR) were calculated using the following formula:

PI (l/m^2 per min) = perfusion flow litres per minute per square metre of surface area

$$\text{TPVR (dynes s cm}^{-5}\text{)} = \frac{[\overline{\text{AP}} - \overline{\text{CVP}}\ \text{(mmHg)}] \times 1332^{*} \times 60}{\text{Perfusion flow (ml/min)}}$$

* 1332 is the factor to convert mmHg to dynes/cm^2. Results are expressed as mean ± SD.

Results

NORMOTHERMIC GROUP

Arterial oxygen tension was 238 ±51 mmHg and carbon dioxide tension was 40 ±8 mmHg. Arteriovenous difference in oxygen saturation was from 30 to 40 per cent and pH value in arterial and venous blood was 7·4 ±0·05 during cardiopulmonary bypass. Mean arterial pressure was maintained above 60 mmHg. However, total peripheral vascular resistance gradually increased with the lapse of perfusion time and in these circumstances administration of phenoxybenzamine was effective in reducing it. But in seven cases in this group where an effective cardiac output could not be achieved after repair of the cardiac anomalies, temporary assisted circulation with the administration of dopamine was instituted. The total peripheral vascular resistance in these patients during administration of dopamine at a constant rate (10 to 30 μg/kg per min) did not increase compared with the patients using phenoxybenzamine only, and they could come off cardiopulmonary bypass in a stable haemodynamic condition (Table 3).

Fig. 1 shows the course of a girl of 4 years and 5 months weighing 18 kg who had an endocardial cushion defect and mitral regurgitation. The ostium primum defect was closed with a pericardial patch and the mitral cleft was repaired by two U-stay sutures. As soon as cardiopulmonary bypass was stopped, she lapsed into low cardiac output, with mean arterial pressure 30 mmHg, central venous pressure 28 cm H_2O, and anuria. Low flow-assisted circulation was carried out twice with the combined use of phenoxybenzamine and dopamine. As a result, effective cardiac output and good urinary output were obtained, and she could be taken off assisted circulation.

HYPOTHERMIC GROUP

The method of deep hypothermia combined with cardiopulmonary bypass was applied in six severe cases whose body weight was about 10 kg. Complete circulatory arrest or extremely low flow perfusion was used in order to make intracardiac operation easier with an oesophageal temperature of 15 to 25°C.

Table 1 *Patient population*

	Normothermia		*Hypothermia*	
	POB	*POB+DA*	*POB*	*POB+DA*
TOF	3	4		
+PDA			1*	
VSD	6	2	1	
+PDA				1
+ASD	1			
+ASD+PS	1			
+PS+AR	1			
+MR				1
+TCRV	1			
ECD				
+ASD			1	
+ASD+PS			1	
+MR	1	1		
Total	14	7	4	2

POB, phenoxybenzamine; DA, dopamine; TOF, tetralogy of Fallot; PDA, persistent ductus arteriosus; VSD, ventricular septal defect; ASD, atrial septal defect; PS, pulmonary stenosis; AR, aortic regurgitation; MR, mitral regurgitation; TCRV, two-chambered right ventricle; ECD, endocardial cushion defect.
* After Blalock's operation.

Table 2 *Method of cardiopulmonary bypass*

	No. of patients	*Body weight (kg)*	*BSA (m^2)*	*Haemodilution ratio (%)*	*Perfusion index (l/m^2 per min)*	*Total perfusion time (min)*	*Minimum body temperature (°C)*	
							Oesophageal	*Rectal*
Normothermia								
POB	14	12·2 ±3·2	0·55 ±0·12	44·5 ±10·9	3·9 ±0·5	102·2 ±28·3	—	—
POB+DA	7	13·7 ±4·0	0·59 ±0·16	34·7 ± 7·3	3·7 ±0·4	105·7 ±21·2	—	—
Hypothermia								
POB	4	10·5 ±3·4	0·46 ±0·15	35·4 ±13·9	3·4 ±0·7	142·0 ±63·2	19·1 ±5·3	21·8 ±5·3
POB+DA	2	8·6 ±2·7	0·41 ±0·08	21·5 ±2·7	3·5 ±2·7	123·5 ±59·5	24·0 ±2·6	26·2 ±0·9

POB, phenoxybenzamine; DA, dopamine; BSA, body surface area.

Table 3 *Serial changes of total peripheral vascular resistance during cardiopulmonary bypass with normothermia*

	Cardiopulmonary bypass				
	15 min	*30 min*	*60 min*	*120 min*	*120 to 210 min*
POB	1749·00 ±477·20 (n=14)	2248·64 ±591·76 (n=14)	1782·21 ±375·02 (n=14)*	2432·83 ±567·41 (n=6)	
POB+DA	1843·43 ±565·08 (n=7)	2180·14 ±684·51 (n=7)	1696·51 ±906·82 (n=7)*	2141·25 ±720·59 (n=7)†	2144·57 ±503·11 (n=4)

POB, phenoxybenzamine; DA, dopamine.

* After drip infusion of 0·5 to 1·0 mg/kg phenoxybenzamine.

† During drip infusion of 10 to 30 μg/kg per min dopamine after additional infusion of 0·5 to 1·0 mg/kg phenoxybenzamine.

Total peripheral vascular resistance increased gradually in proportion to the decrease in blood pressure and body temperature, to about 200 or 300 per cent of normal at 30 minutes of bypass. This returned to about 2000 dynes s cm^{-5} at the time of withdrawal from cardiopulmonary bypass by rewarming and administering phenoxybenzamine. In two patients in this group, however, cardiogenic shock with high total pulmonary vascular resistance and oliguria occurred immediately after cardiopulmonary bypass was stopped, and assisted circulation was carried out with a drip infusion of dopamine at a constant rate (30 μg/kg per min) after the additional administration of phenoxybenzamine (0·5 to 1·0 mg/kg). Assisted circulation for a short time produced sufficient arterial pressure and urinary output, with lowering of total peripheral vascular resistance, for these patients to come off cardiopulmonary bypass (Table 4).

Fig. 2 shows the course of a boy of 19 months (6·7 kg in body weight) with ventricular septal defect, persistent ductus arteriosus, severe pulmonary hypertension, and left superior vena cava. The ductus arteriosus was closed by suture ligation under total circulatory arrest combined with deep hypothermia at an oesophageal temperature of 19°C, and the ventricular septal defect was closed by U-stay suture with a Teflon patch. Phenoxybenzamine was used in a dosage of 0·5 mg/kg at the time of bypass rewarming. As the arteial pressurer decreased gradually and the central venous pressure increased when cardiopulmonary bypass was withdrawn, assisted circulation with the combined use of phenoxybenzamine and dopamine was required for 31 minutes in order to prevent low cardiac output syndrome.

Discussion

During cardiopulmonary bypass a patient is considered to be in a state of pre-shock with a moderate increase in systemic vascular resistance. To combat this, many kinds of vasodilators are used during cardiopulmonary bypass and catecholamines are given frequently after bypass. Among

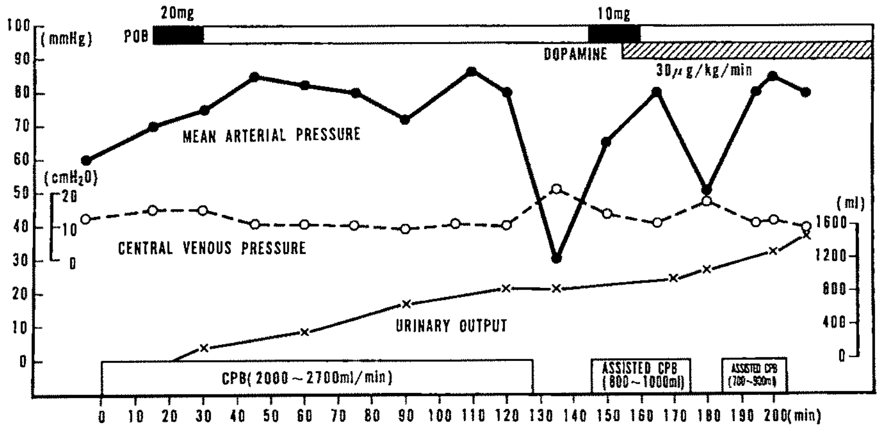

Fig. 1 *Haemodynamic changes during study period of patient HN.*

Table 4 *Serial changes of total peripheral vascular resistance during cardiopulmonary bypass with hypothermia*

	Cardiopulmonary bypass				
	15 min	*30 min*	*45 to 60 min*	*60 to 120 min*	*120 to 210 min*
POB	2718·25 ±626·32 (n=4)	3110·75 ±876·19 (n=4)	2113·75 ±677·25 (n=4)*	2307·33 ±693·02 (n=3)	
POB+DA	3408·50 ±350·02 (n=2)	4073·50 ±939·74 (n=2)	4074·35 ±939·67 (n=2)*	2793·50 ±770·04 (n=2)†	2325·50 ±1276·33 (n=2)‡

POB, phenoxybenzamine; DA, dopamine.
* After drip infusion of 0·5 to 1·0 mg/kg phenoxybenzamine.
† After additional infusion of 1·0 mg/kg phenoxybenzamine.
‡ During drip infusion of 30 μg/kg per min dopamine.

these drugs, it may be appropriate to use phenoxybenzamine or isoprenaline and dopamine.

Isoprenaline produces cardiac stimulation and mesenteric and peripheral vasodilatation by its action on the beta-adrenergic receptors. Currently, it occupies a position of prominence in the treatment of shock syndrome unresponsive to volume expansion, regardless of aetiology.[7–9] On the other hand, phenoxybenzamine is known to increase the cardiac output, stroke volume,[10] and renal blood flow[4] when given intravenously. Alpha-adrenergic receptor blocking drugs such as phenoxybenzamine induce cardiac stimulation mostly because the fall in systemic blood pressure accompanying systemic vasodilatation initiates reflex tachycardia.[5] Because isoprenaline increases heart rate and causes arrhythmia much more often than does phenoxybenzamine,[11 12] we combined phenoxybenzamine with dopamine in patients in the low cardiac output state at the time of withdrawal of cardiopulmonary bypass.

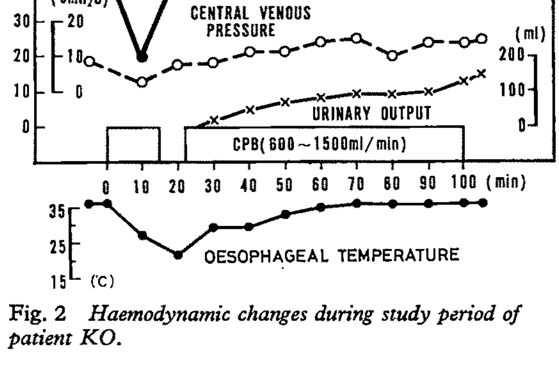

Fig. 2 *Haemodynamic changes during study period of patient KO.*

Many experimental reports have indicated that low doses of dopamine decrease resistance in the renal and mesenteric vascular beds,[13–15] but not in the limb circulation,[2 13] and that higher doses cause predominant vasoconstriction in both visceral and limb vascular beds.[2 13] In addition, many clinical studies indicated that, in adults, low doses (2 to 5 μg/kg per min) caused increased renal blood flow with little effect on heart rate, blood pressure, or myocardial contractility; moderate doses (5 to 15 μg/kg per min) caused increased renal blood flow, heart rate, cardiac contractility, and cardiac output; and high doses (more than 20 μg/kg per min) produced a renal blood flow which might be reduced.[12 16] In infants and children, dopamine is a safe drug when used in moderate doses and is effective in increasing blood pressure and urine production with little change in heart rate and central venous pressure.[17] This unique mechanism responsible for the direct vasodilator effect is believed to be specific to the mesenteric and renal bed.[2 3 13 18] Furthermore, dopamine increases coronary artery blood flow but with relatively less increase in myocardial oxygen consumption and, therefore, increases myocardial efficiency.[13 19] The dose of dopamine (30 μg/kg per min) used in this series is *high* by the above criteria. But as the circulatory blood volume of the patient increased about twofold during cardiopulmonary bypass in which whole blood and diluent (800 to 1500 ml) were primed into oxygenator and extracorporeal circuit, the actual dose of dopamine was considered to be *moderate* (about 15 μg/kg per min). The combined use of phenoxybenzamine and dopamine provided a stable haemodynamic condition without a high total peripheral vascular resistance and stimulated the removal of diluent by good urinary output.

This method is useful in the treatment of the low cardiac output syndrome when coming off cardiopulmonary bypass.

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Br Heart J 1980; **43:** 393–413

Non-invasive diagnosis and assessment of aortic valve disease and evaluation of aortic prosthesis function using echo pulsed Doppler velocimetry*

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SUMMARY Non-invasive recording of aortic blood flow velocity patterns in the ascending aorta and in the arch of the aorta was performed in 12 normal subjects, 38 patients with confirmed aortic valve disease, and 13 patients with aortic prostheses using pulse echo Doppler velocity recordings. In normal subjects, the velocity recordings correlated well with those obtained by other authors using invasive procedures. In patients with aortic valve disease, specific abnormalities of the velocity curves were found to correlate well both with the type of lesion (stenosis or regurgitation) and its severity on a three-point scale. Both sensitivity and specificity were found to range between 80 and 94 per cent. A less accurate grading of severity was obtained from patients with aortic regurgitation by the detection of turbulence in the left ventricular outflow tract than from the appearance of the aortic velocity curves. In the studies of patients with aortic prostheses, anomalies of the velocity pattern could be found in the ascending aorta in 53 per cent but no abnormalities of timing were found.

In spite of some technical limitations, pulse echo Doppler velocity recordings provide a new non-invasive, reliable, and reproducible approach in assessing the presence and severity of aortic lesions and demonstrating flow abnormalities produced by prostheses.

The accurate diagnosis and assessment of the severity of aortic valve disease as well as malfunction of aortic valve prostheses require invasive procedures. None of the non-invasive techniques such as phonocardiography, continuous wave Doppler arterial blood velocity measurements, or standard echocardiography can give a full evaluation of aortic valve function in all types of lesion. Two-dimensional echocardiography, though helpful in many lesions, is not sufficiently accurate in the assessment of aortic regurgitation and does not by itself provide useful information about flow dynamics of the aortic valve. The recent development of pulse echo Doppler blood velocity recordings by our group[1–3] enables the clinician to record directly and non-invasively the flow velocity patterns in the aorta and prompted us to find out whether it could provide a useful technique for the evaluation of aortic valve function.

Subjects and methods

The control group consisted of 12 healthy subjects (four female and eight male), ranging in age from 5 to 54 years (mean 24), in whom any suspicion of organic heart disease had been ruled out by standard non-invasive procedures. A group of 38 subjects with aortic valve disease was studied (11 female and 27 male) ranging in age from 13 to 77 years (mean 49), including 11 with pure aortic stenosis, 17 with pure regurgitation, and 10 with combined stenosis and regurgitation (Tables 1–3). The aetiology of the aortic stenosis was found to be rheumatic in six cases, congenital in five cases, and degenerative with calcification in 10 cases. The aetiology of the aortic regurgitation was rheumatic in 10 cases, endocarditis in two cases, aortic dissection in one case, congenital in one case, atheroma in one case, and paravalvular prosthetic leak in one case. There was also one case of Pezzi-Laubry syndrome.

Four of these cases had associated mitral valve lesions, and two had mitral prostheses; 31 were in sinus rhythm, five had atrial fibrillation, one ventricular paced rhythm, and one second degree atrioventricular block. Five patients had left bundle-branch block. The diagnosis and assessment of the severity of these lesions were confirmed in all cases, either by retrograde left heart catheterisation or at the time of surgery, or both. Twenty patients

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* Partly supported by a grant from INSERM (CNAMTS)

Received for publication 20 August 1979

Table 1 *Haemodynamic and surgical data of patients with aortic stenosis*

Case no.	*Rhythm*	*LV pressure (mmHg)*		*Aortic pressure (mmHg)*		*CI (l per min per m^2)*	*Aortography*	*Volume of regurgitation % CO (DDC)*	*Aortic valve area (cm^2) (catheterisc tion or surgery)*
		S/D	*ED*	*S/D*	*Mean*				
1	SR	NP		120/70	90	2·4	AS		0·30
2	SR	NP		120/67	86	2·9	AS	<5	
3	SR	204/4	10	116/60	82	2·8	AS	<5	0·50
4	SR	NP		106/68	88	3·0	AS	<5	0·30
5	SR	NP		174/88	122	3·3	AS		0·15
6	SR	NP		120/60	80		AS	<5	1·0
7	SR	NP		110/66	84	1·5	AS		0·2
8	SR								
9	SR								2·25 (post-valvotomy)
10	AV block	114/0	4	100/60	78	2·6			1·55
11	PM	NP		135/52	88	1·9			1·0

SR, sinus rhythm; AV, atrioventricular; PM, pacemaker; LV, left ventricle; S/D, systolic/diastolic; ED, end-diastolic; CI, cardiac index; CO, cardiac output; DDC, dye dilution curves; MS, mitral stenosis; MR, mitral regurgitation; NP, left ventricle catheterisation not possible.

Table 2 *Haemodynamic and surgical data of patients with aortic regurgitation*

Case no.	*Rhythm*	*LV pressure (mmHg)*		*Aortic pressure (mmHg)*		*CI (l per min per m^2)*	*Aortography*	*Volume of regurgitation % CO (DDC)*
		S/D	*ED*	*S/D*	*Mean*			
12	SR	80/10	25	80/50	65	2·1	+++	
13	AF							
14	SR	115/0	15	145/55	100	1·5	+++	
15	SR	200/0	5	200/140	90		+++	
16	SR	170/5	30	165/50	85		++	
17	SR	130/4	8	125/45	80	2·7	+++	
18	SR	132/0	26	130/82	45	1·7	++	31
19	SR	145/2	7	145/66	105	2·9	++	40
20	SR	200/0	8	200/72	125	2·8	++	30
21	SR							
22	AF	125/0	10	125/75	90		++	
23	AF	130/8	2	125/25	70	2·7	+++	
24	SR	170/6	26	170/90	122	2·4	+	15
25	SR							
26	SR	145/2	10	140/45	80	2·2	++	40
27	AF	115/0	10	115/45	80	1·9	++	
28	AF	120/2	4	105/55	80	2·1	+	20

AF, atrial fibrillation; VSD, ventricular septal defect; Mit. pr., mitral prosthesis; ASD, atrial septal defect. Other abbreviations as in Table 1.

Table 3 *Haemodynamic and surgical data of patients with associated aortic stenosis and regurgitation*

Case no.	*Rhythm*	*LV pressure (mmHg)*		*Aortic pressure (mmHg)*		*CI (l per min per m^2)*	*Aortography*	*Volume of regurgitation % CO (DDC)*	*Aortic valve area (cm^2) (catheterisation or surgery)*	*Surgery*
		S/D	*ED*	*S/D*	*Mean*					
29	SR									+
30	SR									+
31	SR	180/10	22	160/110	80	2·8	++		1·0	+
32	SR	112/0	5	100/55	65	2·3	+		1·0	+
33	SR	220/0	28	185/90	120		++		1·2	–
34	SR								0·9	+
35	SR	190/4	20	180/60	104	2·2	+++	45	1	+
36									0·4	+
37	SR	NP		130/64	90	2·5	++	35		+
38	SR	NP		114/56	80	2·3		17		+

CAS, coronary atherosclerosis. Other abbreviations as in Tables 1 and 2.

Surgery	*Aortic stenosis grading*	*Associated lesions*	*Aetiology*
+	3		Calcified degenerative
+	3		Calcified bicuspid valve
+	3		Calcified degenerative
+	3		Calcified degenerative
+	3	Renal insufficiency	Calcified dengenerative
+	2		Calcified degenerative
+	3		Calcified bicuspid valve
+	3		Calcified degenerative
– (previ. commissurotomy)	1		Congenital stenosis, post-commissurotomy
–	1	MS + MR	Rheumatic
+	2	MS + MR	Calcified, rheumatic

Surgery	*Aortic regurgitation grading*	*Associated lesions*	*Aetiology*
+	3		Infective endocarditis
+	1	MS	Rheumatic
+	3	VSD	Pezzi-Laubry SD
+	3		Rheumatic
+	2		Rheumatic
+	3		Rheumatic
+	2		Rheumatic
+	2		Rheumatic
+	2		Rheumatic
+	3		Infective endocarditis
–	2		Rheumatic
–	3		Rheumatic
–	1	Cardiomyopathy	Degenerative
+	3	Mit. pr.	Prosthesis disinsertion
–	2		Dissecting aorta
+	2		Rheumatic
–	1	ASD	Congenital

Aortic stenosis grading	*Aortic regurgitation grading*	*Associated lesions*	*Aetiology*
2	1		Rheumatic calcified
2	1		Calcified degenerative
2	2	Mit. pr.	Rheumatic calcified
2	1	MS + MR	Rheumatic
2	2	CAS	Calcified degenerative
2	1		Bicuspid calcified valve
2	3		Bicuspid calcified valve
3	1		Calcified rheumatic
2	2		Calcified degenerative
2	1	CAS	Calcified degenerative

had retrograde left heart catheterisation using a Telco manometer, 26 cases had aortography and/or dye dilution curves with indocyanine green (13 cases) using the Waters apparatus, and 30 patients were assessed at the time of operation. Cardiac output was measured by the dye dilution technique. There was a third group of patients with aortic valve prostheses, ranging in age from 12 to 73 years (mean 40), of whom nine had a Starr-Edwards prosthesis, two a Björk-Shiley prosthesis, one a Lillehei-Kaster prosthesis, and one a Hancock prosthesis. Of these 13 patients (four female and nine male), four also had a mitral prosthesis. A fourth group of 13 subjects with heart disease not involving the aortic valve (eight female, five male) ranged in age from 8 to 62 years (mean 37); three had pulmonary stenosis, three had mitral stenosis, two had ventricular septal defects, and one had an atrial septal defect. One of these patients had isolated right bundle-branch block and one had arterial disease involving the lower limbs. There was also one with hypertrophic cardiomyopathy and one with Fallot's tetralogy.

CLASSIFICATION OF PATIENTS WITH AORTIC VALVULAR DISEASE

Three grades of severity were used: 1 (mild); 2 (moderate); 3 (severe). The classification of the pure or predominant lesion on this three-point scale was based partly on the symptoms and on the clinical presentation (bedside examination, chest *x*-ray, electrocardiogram, and clinical course) and partly on the haemodynamic and/or the surgical data. In the patients with aortic stenosis, the grading was based on the calculated aortic valve area assessed either by the findings at cardiac catheterisation using the Gorlin formula[4] (valve area greater than 1·5 cm^2 for grade 1, from 0·8 to 1·5 cm^2 for grade 2, and less than 0·8 cm^2 for grade 3), with correction for any aortic regurgitation proven by aortography or dye dilution. In some cases the left ventricular aortic gradient could not be measured as at the time of left heart catheterisation the aortic valve could not be crossed. In some instances when the patient was very ill, no cardiac catheterisation data were available as the patient went straight to surgery. In these cases, the degree of stenosis was evaluated from assessment of the appearance of the valve by the surgeon who took into account the severity of the commissural fusion and estimated the approximate area for the valve obtained from two-dimensional measurements. Four cases of tight calcific stenosis associated with insignificant regurgitation (less than 5% on the dye dilution curves) were considered as pure stenosis (cases 2, 3, 4, and 6). Aortic regurgitation was assessed by dye dilution curves[5] ($<20\%$ of systemic output = grade 1; 20 to 40% = grade 2; $>40\%$ = grade 3) or by aortography (+ = slight regurgitation disappearing at the next systole; ++ = regurgitation with opacification of the ventricle still present at the next systole, with progressive opacification of the left ventricle; +++ = immediate total left ventricular opacification). Surgical findings were also taken into account whenever appropriate. The three-point scale aortographic classification was used to avoid possible overlap between the grades when using a four- or five-point scale.[6 7] This was to avoid a statistically significant risk of erroneous grading being introduced.[8] The same three-point grading was used for associated lesions. Since this group of patients studied included few mild lesions, 10 additional subjects, five with mild aortic stenosis and five with mild aortic regurgitation, were also studied to test the validity of the method. The diagnosis was assessed by other non-invasive procedures and on the clinical data including electrocardiography, chest *x*-ray, phonocardiograms, and echocardiograms. However, these additional cases were not included in the statistical analysis.

TECHNIQUE

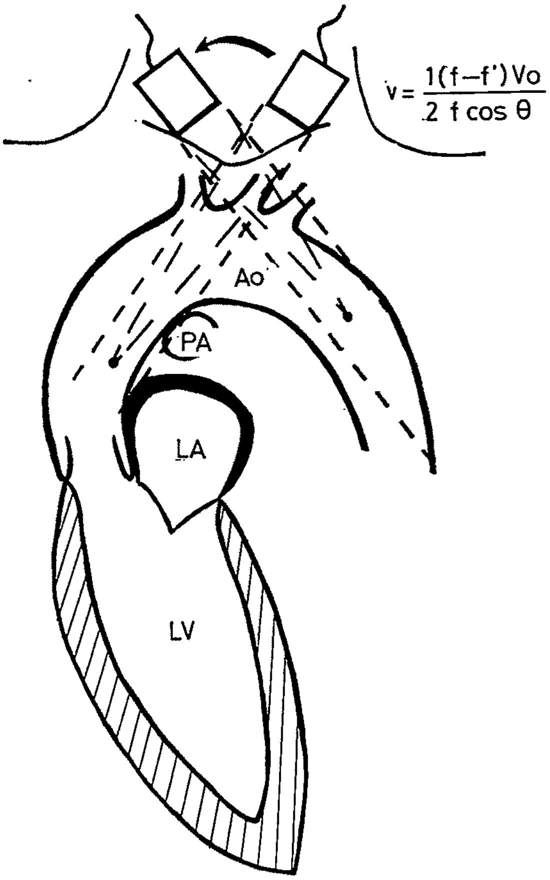
Range-gated ultrasonic pulsed Doppler blood velocity recording technique has been described elsewhere,[9 10] particularly the principle, apparatus, and the combined use of the Doppler technique with echocardiography using spectral analysis.[11]

(A) *Doppler principle*

The instantaneous flow velocity of a small (2 × 4 mm) teardrop-shaped sample volume of blood is proportional to the frequency shift between the ultrasonic beam emitted to, and the back-scattered ultrasound from, the red blood cells within the sample (Fig. 1). A range-gating system makes it possible to pick up any desired sample volume along the axis of the ultrasound beam within the limits of the equipment (3 to 17 cm).

(B) *Apparatus*

The ATL 500A blood flowmeter was used, combining a 3 MHz velocimeter which emits brief pulses (1·0 to 1·5 μs) at a pulse repetition of frequency of between 2 and 15 kHz (depending on the depths of the sample volume) and an echocardiograph having A- and M-mode. The echocardiograph and the Doppler recordings are made with a single transducer 1·2 cm in diameter. The output signal from the Doppler equipment is an audio signal which is fed to two loudspeakers and a spectral frequency display which consists of a time interval histogram. Additionally, our apparatus is equipped with an analogue velocity output obtained by frequency to voltage conversion of the audio signal using zero crossing detection technique. This equipment was used in our studies of the mitral valve.[2] The analogue velocity output can be



Transcutaneous aortic flow velocimetry
(pulsed Doppler-echo)

Fig. 1 *The velocity of a small sample of blood is recorded at the same time as an echocardiogram which locates the position of the sample volume (echo shown by parallel dashed lines). The blood velocity is recorded according to the Doppler principle equation, upper right. Note the almost parallel orientation of the ultrasound beam and the long axis of the vessel minimising theta in the Doppler equation. The transducer is orientated downwards and is swept from the right anterior position for recording blood velocity in the ascending aorta to a left posterior position for recordings from the aortic arch. Depending on the depths of the range gate, several sample volumes may be obtained ranging along the ascending aorta and the arch. Ao, aorta; PA, right pulmonary artery; LA, left atrium; LV, left ventricle.*

recorded simultaneously or separately on a strip-chart recorder and demonstrates more obviously the anomalies which are also seen on the time interval histogram but are less easy to measure and evaluate on that type of display. The analogue velocity output represents a more convenient way of demonstrating cardiovascular correlation and is especially useful for grading the severity of lesions. The use of pulse echo techniques with limited pulse repetition frequency means that the maximum velocity that can be measured is limited and the true value of the flow velocity in the highly turbulent flow regimens seen in aortic valve disease is underestimated. The zero crossing technique to obtain an analogue blood velocity curve also results in underestimation of the flow velocity where there is a poor signal to noise ratio. It is therefore worth emphasising that the method described relies exclusively on pattern recognition and time anomalies in the flow velocity curves and not on the absolute value of velocity measured by this technique. The timing of the flow velocity characteristics was made from the analogue curve because they were easier to recognise there, but these measurements were always checked against the simultaneous time interval histogram spectrogram to make sure there was no distortion of the readout. The approximate time delay introduced by the frequency to voltage converter was approximately 30 ±0·3 ms when it was compared with the output from an electromagnetic flowmeter. Because of this delay in the velocity curve, the relative value and the absolute value of measurements were considered and compared with each other rather than made into absolute measurements. The ATL equipment includes a conventional echocardiograph with display of both A- and M-mode. A single transducer is used for all procedures; the location of the Doppler gate which controls the position of the sample volume is controlled by the operator and can be monitored on an oscilloscope. The device is linear to within 5 per cent from 0 to 100 cm/s for steady flow.

RECORDING TECHNIQUE

Echo-Doppler recordings include either simultaneously or separately the analogue velocity curve, spectral display, and M-mode echocardiogram showing the cardiac structures or major vessels. The recordings were made on an eight-channel photographic Irex recorder, together with lead II of the electrocardiogram, and a frequency selected phonocardiogram. Recordings were made at a chart speed of 50 or 75 mm/s, and the timing markers are at intervals of 40 ms. The tracings were recorded during apnoea or light respiration, with the patients lying flat on their backs initially with the head slightly extended and eventually with the shoulders raised on a pillow. Recordings were made most conveniently from the aorta with the transducer coated with conductive jelly placed in the suprasternal notch perpendicular to the skin so that the ultrasound beam successively passed through the aortic arch, the right pulmonary artery, and the left atrium[12] (Fig. 2). The transducer is then slightly angulated in a left posterior right anterior plane to superimpose both the axis of the ultrasound beam and the aorta. The Doppler gate is then adjusted to lie within the lumen of the vessel (Fig. 1). The correct orientation has been achieved when the typical Doppler audio signal is heard with minimal gain settings. It is possible by tilting the transducer and altering the depth of the sample volume to record several velocity wave forms at different sites within the ascending aorta and aortic root. The convention is followed of showing flow away from the left ventricle as a positive deflection and flow back towards the left ventricle as a negative deflection. This flow convention can be maintained by reversing a polarity switch when recordings are being made from the arch or descending aorta as opposed to the ascending aorta since the direction of flow with respect to the Doppler probe changes. Another approach to the ascending aorta is from the right supraclavicular fossa. From this site, the sample volume is set to depths from 5 to 8 cm. At 8 or 9 cm, the sample volume is very close to the sinuses of Valsalva. In that situation some of the aortic valve may be seen on the echocardiographic trace and a sharp sound may be superimposed on the Doppler audio signal if the valve enters the Doppler sample volume. A third approach is from the conventional echocardiographic access point along the left sternal edge. This approach is particularly useful for recording aortic valve motion velocities, turbulence, and prosthetic motion velocities, whereas aortic blood velocities are poorly recorded from this site as the ultrasound beam is almost at right-angles to the flow. A specific search for turbulence in the left ventricular outflow tract was always made in cases of pure aortic regurgitation to verify the site of regurgitation and prove that it was the aortic orifice.[11]

FEATURES OF VELOCITY RECORDINGS

Velocity patterns

In every recording from the ascending aorta and arch, we carefully studied: (1) the shape of the systolic "S" summit of the systolic curve; (2) the band width of the frequency spectrum; and (3) the pattern and polarity of the diastolic curve.

Timing

The following time intervals were measured on the velocity curves obtained from measurements from the ascending aorta and arch; RR intervals of the electrocardiogram; Q wave of the electrocardiogram to the onset of the systolic velocity curve (Q–O). The ejection time was determined from the analogue velocity (zero-crossing output) from the beginning to the end of the systolic wave. Three successive measurements were made from every subject and the average value thus obtained. All the time intervals were expressed in milliseconds and corrected for heart rate according to the Bazett formula.[13] In this series of 76 patients, from whom two basic recordings were made (total 152), 32 could not be used for timing measurements because of inadequacy of either the time interval histogram recording or the analogue signal. A statistical analysis of the results was performed using a Hewlett-Packard A851 computer used to derive mean values and standard deviations and also to perform Student's t test between the different groups of subjects.

Results

Timing data are summarised in Table 4.

The curves represent the blood velocity patterns of aortic blood flow at different points in the aorta. Since the output of the Doppler device is directional, negative flow, that is flow back towards the

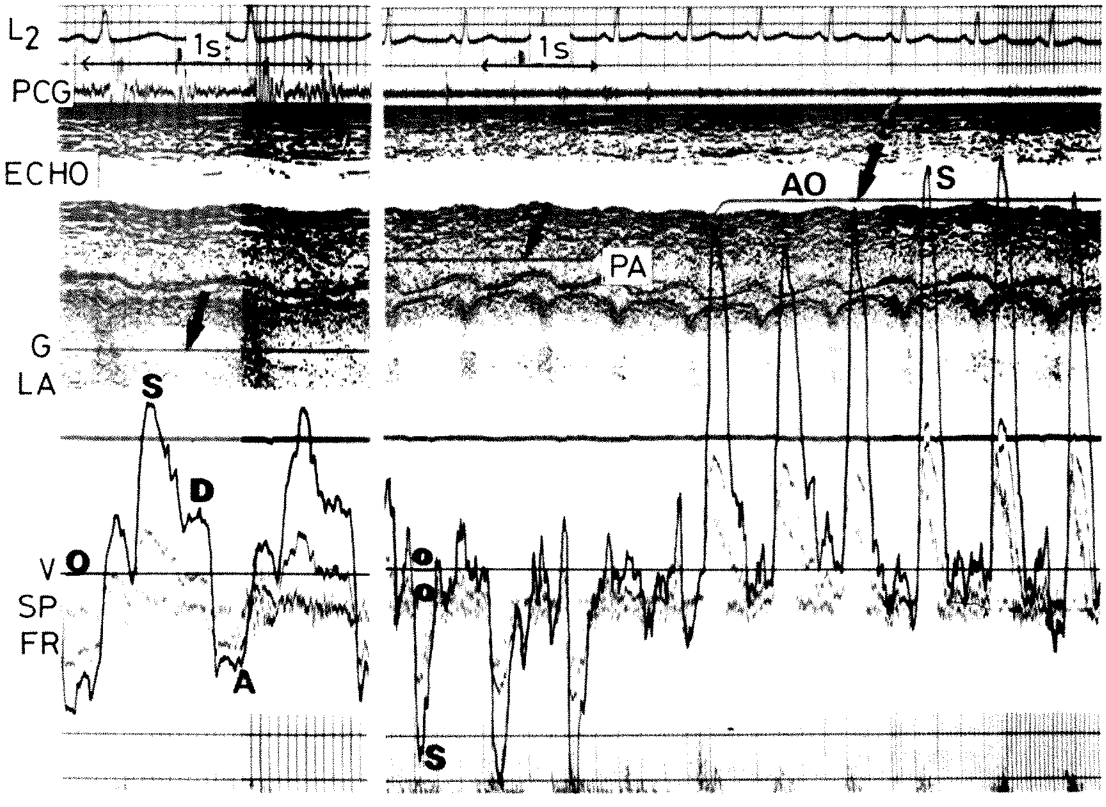


Fig. 2 *Suprasternal echo-Doppler scanning from the left atrium to the aorta in normal subjects. From above down, lead II ECG phonocardiogram (medium high frequency); echo with the sample volume position shown by "G" and at the bottom the analogue flow velocity output superimposed on the spectral display (FR). The sample volume position "G" is shown on the echocardiogram for successive recordings from the left atrium (LA) depth 9 cm: a high atrial velocity pattern is displayed on the left; next in the right pulmonary artery (PA) depth 7 cm: a negative systolic wave away from the transducer is recorded in the middle, and finally in the aorta (AO) depth 6 cm, a positive systolic wave towards the transducer of much higher amplitude is recorded here. A spectral negative S wave indicating aortic arch location of the sample is often shown using this orientation, but this is dependent upon the anatomy of the subjects.*

left ventricle is shown as a negative curve and flow away from the heart as a positive deflection.

NORMAL SUBJECTS (Group 1: Fig. 2, 3, and Table 4)

(1) *Ascending aorta*

The pattern of the spectral curve starts at the end of the first sound, and consists of a large positive triangular-shaped systolic wave, with a rapid upstroke, a sharp early peak labelled "S" followed by a less rapidly descending limb. It overrides the zero line and shows a precipitous, much smaller, negative deflection labelled the "R" wave. The velocity curve then rejoins the zero line and follows it throughout the remainder of diastole, showing a few small oscillations. The spectral output is made up of a thin regular coherent line of dots very closely spaced. The breadth of the spectrum is usually less than 1 cm, with discrete broadening of the spectrum at the top or on the descending limb of the summit "S". Small variations may occur consisting of a bifid pattern of the "S" wave or an irregular "S" summit amplitude, depending directly on the length of the preceding diastole in the case of a respiratory arrhythmia. When recordings have been made from close to

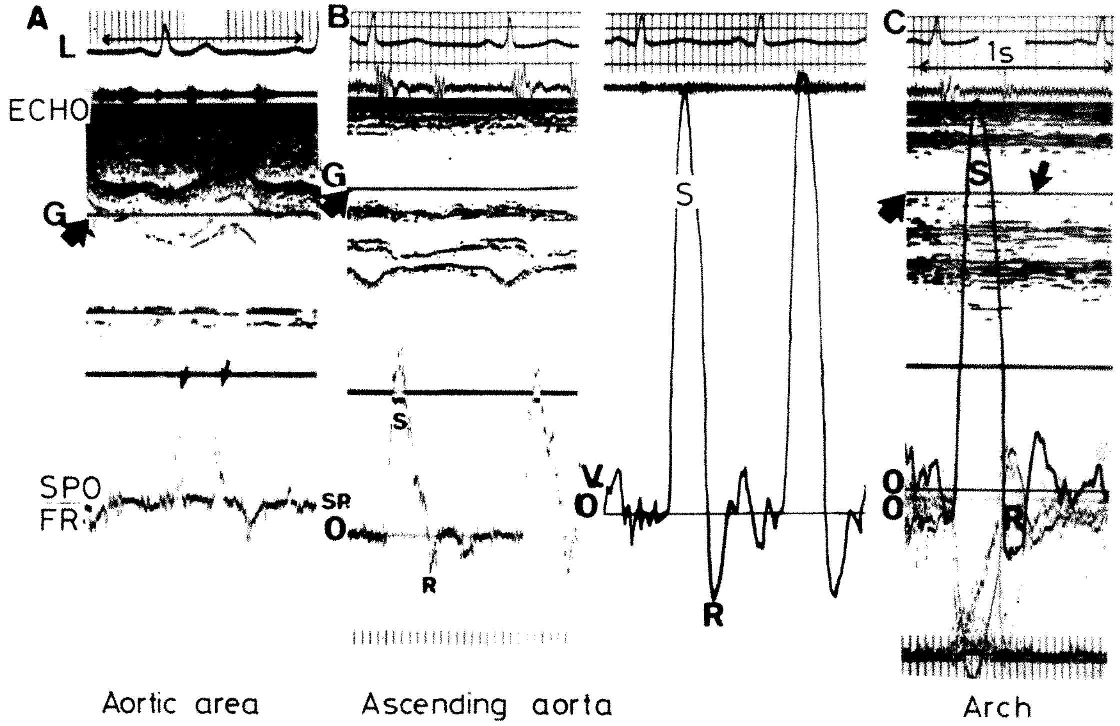


Fig. 3 *Normal subject.* (A) *Normal aortic orifice (from top to bottom: lead II of the electrocardiogram; ECHO echocardiogram; G, velocimetric gate with oblique arrows, SP, FR, frequency spectrum). The visualisation of the gate (horizontal line) in the centre of the aortic orifice documents the position of the Doppler signal. The spectrum frequency displays two thin and brief deflections (thin arrows), synchronous with the opening and closing of the aortic valves, generally having the same positive sign.* (B) *Normal flow velocity pattern in the ascending aorta (same legend as Fig. 2). With the gate (G) located in the aorta, a large systolic positive wave "S" is displayed on the spectral (left) as well as on the analogue (right) curve, documenting the location of the sample in the ascending aorta. Note the slower descending limb of the "S" summit corresponding to a slight physiological broadening of the spectrum, followed by a small brief reversal negative wave, "R". The amplitude of the "S" wave depends on the length of the preceding diastole.* (C) *From top to bottom: lead II of the ECG; PCG, phonocardiogram in medium high frequencies; SP, FR, spectrum frequency; V, analogue flow velocity curves with their respective zero. The gate is located in the aortic arch, as proven by the presence of a large negative systolic wave (flow velocity away from the transducer) on the spectral display: the pattern is similar to that seen in the ascending aorta. For the sake of a more physiological presentation, the convention is followed of showing flow away from the aortic valve as a positive deflection. The analogue curve is therefore reversed with respect to the spectral display.*

Table 4 *Aortic flow velocity timing data for normal subjects, patients with aortic valve disease, patients with aortic prosthesis, control group of cardiac patients*

Group		*HR/min*	*Ascending aorta*		*Aortic arch*	
			Q – O *(ms)*	*ET* *(ms)*	*Q – O* *(ms)*	*ET* *(ms)*
1	Normal subjects	79 ± 16	130 ± 25	328 ± 33	136 ± 17	318 ± 25
2	A = AS	64 ± 15	131 ± 36	361 ± 49	178 ± 28	373 ± 52
	p				< 0·01	< 0·02
AVD	B = AR	73 ± 15	134 ± 22	311 ± 34	153 ± 22	319 ± 43
	C = AS + AR	68 ± 9	138 ± 29	352 ± 45	175 ± 15	342 ± 53
	p				< 0·01	
3	Patients with Ao. pr	76 ± 12	137 ± 23	312 ± 46	142 ± 16	324 ± 32
4	CCG (without AVD)	71 ± 19	136 ± 24	317 ± 37	153 ± 27	312 ± 31

AVD, aortic valve disease; AS, aortic stenosis; AR, aortic regurgitation; Ao. pr, aortic prosthesis; CCG, cardiac control group; HR, heart rate; Q – O, Q to onset of the velocity curve time interval; ET, ejection time; ms, millisecond; p, p value; only the values of p under 0·05 are indicated in this Table.

the aortic valve, a negative diastolic wave is usually recorded but this disappears further away from the valve in the higher ascending aorta. The analogue velocity output shows the same triangular-shaped positive wave with broadly similar characteristics to the spectral display. The corresponding Doppler audio signal heard through the loudspeakers is short, exclusively systolic, and soft.

(2) *Arch*

The patterns are similar to those of the ascending aorta. Since the aortic flow is moving away from the transducer, the systolic deflection of the spectral analysis is negative (the polarity has not been reversed).

(3) *Aortic orifice*

A double sharp brief high-pitched Doppler sound may be heard in the loudspeaker, and on both the analogue and spectral velocity displays a short deflection synchronous with the cardiac sounds is shown. Between these two deflections, often having the same polarity, there is a narrow band width signal though there may be some dispersion of the dots on the time interval histogram.

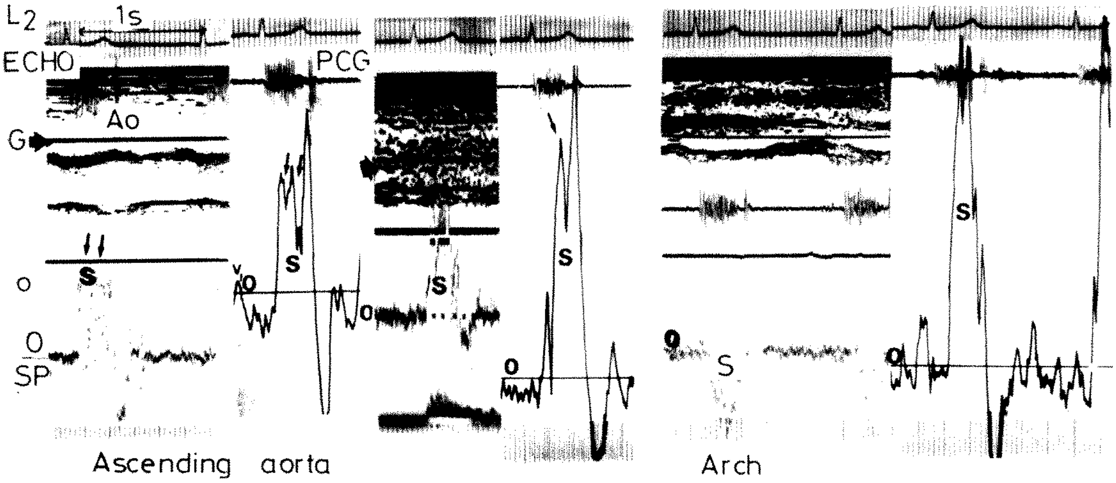


Fig. 4 *Mild aortic valvular stenosis (case 9, postoperative examination of a patient who underwent valvotomy for congenital aortic stenosis with a postoperative aortic area of 2·25 cm²) (same legend as Fig. 3A and B).*
Left: *velocity records in the ascending aorta as shown by the gate (G) and by the positive "S" wave on the spectrum frequency: both the analogue and the spectral curves show characteristic systolic anomalies consisting of the occurrence of coarse and important irregularities (arrows) replacing the normal triangular-shaped "S" wave, when the sample is near the aortic orifice; at a distance along the upper part of the ascending aorta (middle), the "S" summit progressively reappears with a slow and somehow irregular ascent, both on the spectrum and analogue.*
Right: *the gate is in the arch (negative systolic wave on the spectrum). The analogue curve is nearly normal, with a normal upstroke of the "S" wave. However, discrete irregularities are seen on its descending limb, as well as a discrete broadening of the corresponding part of the spectrum. The time delay between the Q-onset of the velocity curves in the ascending aorta and in the arch equals 0·04 s.*

PATIENTS WITH AORTIC VALVE DISEASE
(Group 2: Tables 1–4)

Aortic stenosis (Group 2A: 11 patients, Fig. 4 and 5)
Pattern and timing anomalies were found but only the former are described here.

(1) *Ascending aorta*
The normal triangular systolic pattern is not recorded but is replaced on the spectral display by a wide band width, a signal with considerable dispersion of the dots throughout most, or all, of systole. A slow ascent may be observed on the analogue output. Corresponding anomalies are that the "S" summit is amputated and replaced by an irregular saw-toothed plateau and on the loudspeakers, a loud, harsh prolonged sound is heard. These characteristic anomalies are usually recorded close to the aortic valve and spread a variable distance along the aorta.

(2) *Arch*
The systolic pattern may be very similar to that recorded in the ascending aorta consisting on the time interval histogram of a broadened spectrum and on the analogue display of an amputated saw-toothed summit, or the normal triangular-shaped systolic wave may reappear after a slower than normal ascent. The duration of the systolic wave is usually increased and the tracings frequently overlap in diastole.

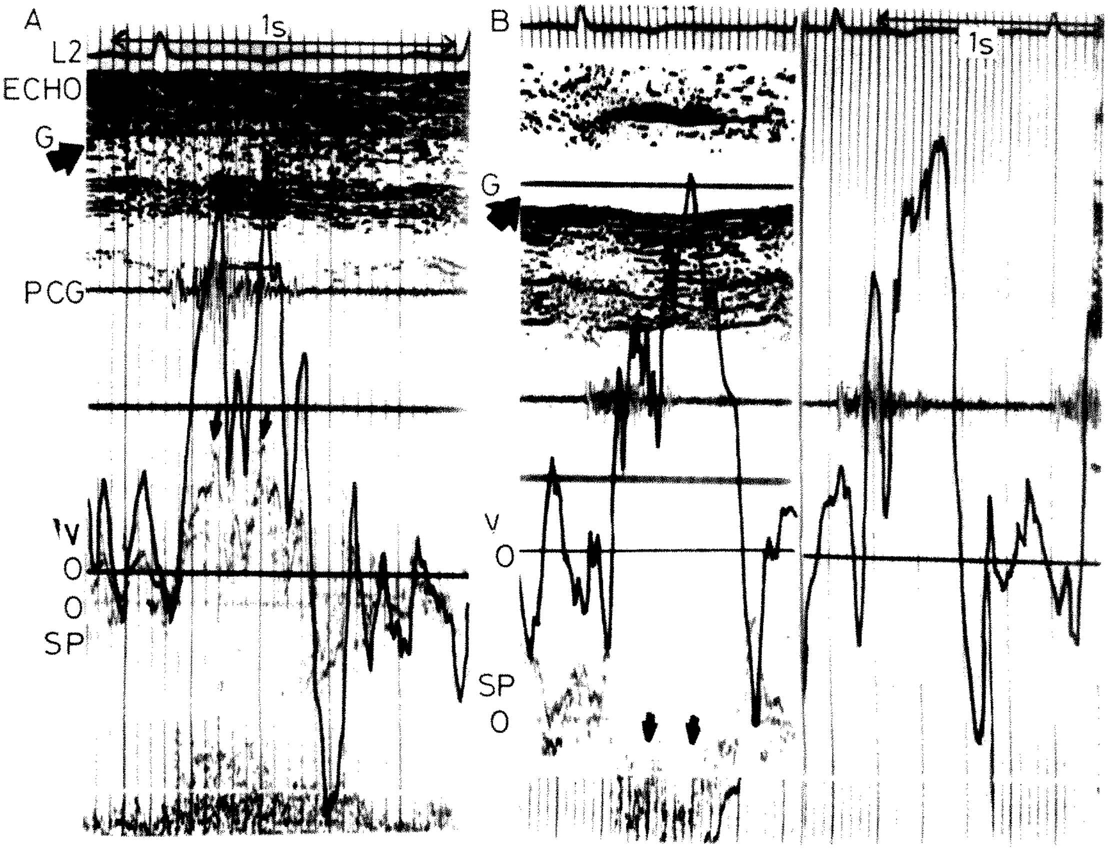


Fig. 5 *Aortic flow velocity pattern in pure and severe aortic stenosis (case 1—aortic orifice of 0·3 cm² at operation) (same legend as Fig. 2 and 3C).*
(A) *The gate (G) is in the ascending aorta. The normal summit "S" is cut off and replaced by the same coarse indentations as seen in the ascending aorta in the preceding case and a large broadening of the spectrum (depth recording 8 cm).* (B) *The gate is in the aortic arch, as proven by the negative systolic wave displayed on the spectrum: the same abnormal pattern is recorded in systole, with no reappearance of the "S" summit. Time delay between the Q-onset of the velocity curves in the ascending aorta and in the aortic arch equals 0·06 s.*

(3) *Aortic orifice*
The loudspeaker sound is loud and harsh in systole. The time interval histogram spectral display shows a wide rectangular-shaped dispersion of the dots spreading all over systole which is synchronous with the external murmur recorded on the phonocardiogram, where the brief initial and final deflections may be unrecognisable (see Fig. 9).

Severe stenosis (seven patients)
In these cases the abnormality found in the ascending aorta seems to spread further into the arch and is seen on both the spectral display and the analogue readout. There is delay in appearance of the systolic wave in the arch of the aorta; spectral broadening and indentations in the analogue velocity output occur very early in the ascending limb. Some of the curves show pronounced diastolic overlap with severe prolongation of the ejection time in four cases.

Mild stenosis (two proven cases and five non-invasively diagnosed cases), and
Moderate stenosis (two cases)
In all these cases except two (case 10 and one externally diagnosed), the characteristic features were present on the velocity curves recorded close to the aortic valve with a delay in the onset of the velocity curves in the aortic arch. However, the velocity anomalies progressively disappear with distance from the aortic valve, as can be seen from recording in the ascending aorta and in the arch (Fig. 4).

REGURGITATION (Group 2B: 17 patients, Fig. 6, 7, 8)
The characteristic anomaly consists of reversed flow in diastole shown as a reversed deflection on both the spectral and analogue curves.

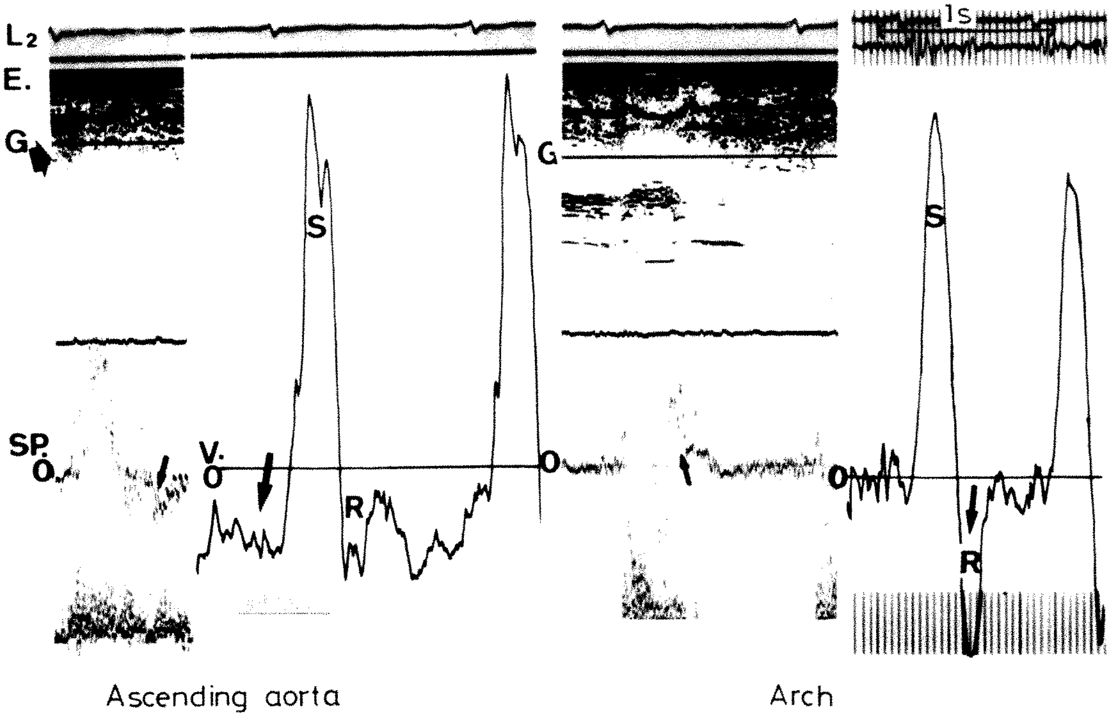


Fig. 6 *Aortic flow velocity patterns in pure and mild aortic regurgitation (case 24—same legend as Fig. 3B).*
Left: *in the ascending aorta, there is an abnormal negativity (oblique arrow) after the initial reversal wave, both on the spectrum and analogue.*
Right: *in the aortic arch, the diastolic pattern is nearly normal, except for a slightly wider reversal wave, followed by a discrete negativity on the analogue. There is no abnormal delay between the respective onsets of both curves.*

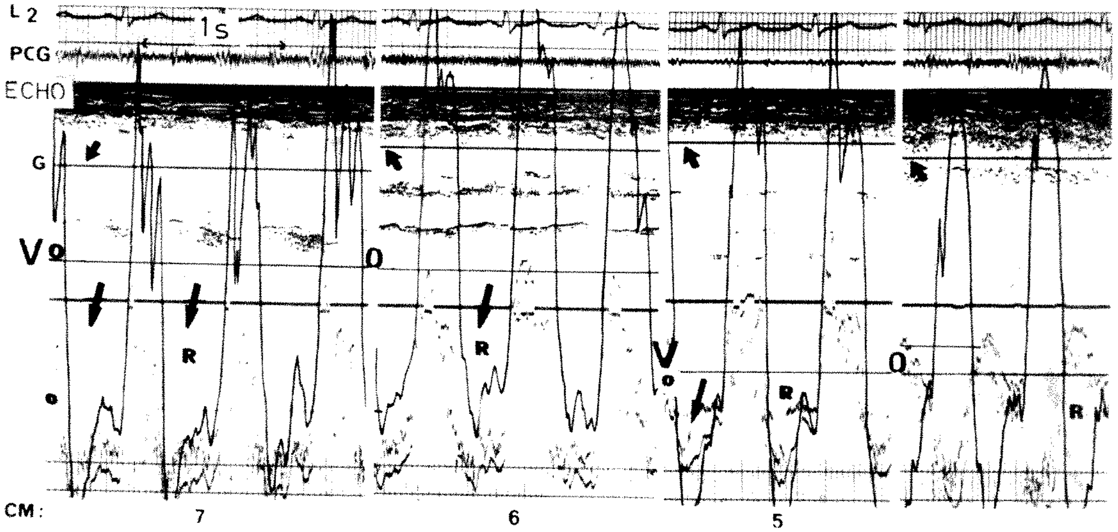


Fig. 7 *Aortic flow velocity patterns in pure and moderate aortic regurgitation (case 20, same legend as Fig. 2). The numbers below the traces indicate the depths of the sample volume from the skin. At 7, 6, and 5 cm velocity traces are recorded in the ascending aorta as the gate is moved progressively downstream from the aortic valve. The diastolic negative velocity deflection becomes progressively less pronounced. The zero calibration is shown in all the traces and moves downwards from left to right. The right-hand trace obtained in the aortic arch has much less reverse flow in diastole on the analgue velocity curve. Though the peak of the systolic curves show some irregular indentations, organic aortic stenosis can be ruled out by the timing of the onset of the systolic velocity wave S.*

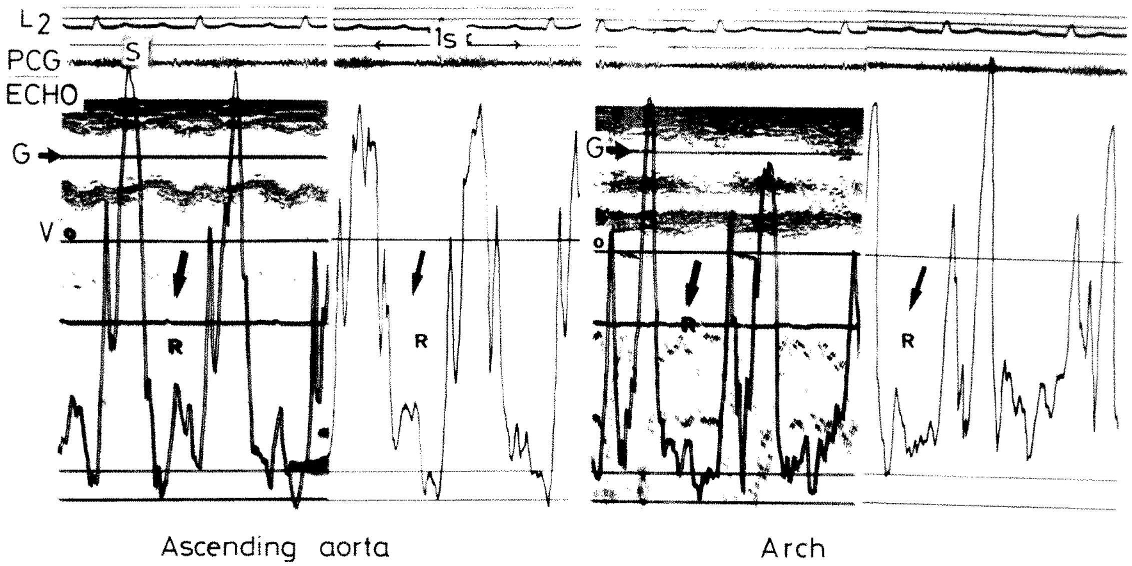


Fig. 8 *Aortic flow velocity patterns in pure and major aortic regurgitation (case 14—same legend as Fig. 2 and 3B).*
Left: *ascending aorta. Note the conspicuously pan-diastolic negative wave ("R" oblique arrows) whose amplitude exceeds that of the systolic wave. The irregular pattern of the "S" wave is often seen in major regurgitation.*
Right: *in the arch. There is still a distinct diastolic negative wave of considerable amplitude and duration. The bifid systolic pattern could be a result of an artefact, but is consistent with the classical systolic pattern seen in aortic regurgitation. No abnormal delay on the Q-onset interval.*

(1) *Ascending aorta*

In diastole, the anomaly is either a simple increase in the width of the physiological early diastolic reverse flow wave or a conspicuous negative wave of variable depth occurring for part or all of diastole. In the time interval histogram display, there is variable spectral broadening. The "S" wave may be normal or show some spectral broadening and in the analogue curve a bifid or indented pattern. The Doppler audio signal heard on the loudspeaker has a "to-and-fro" tone resulting from an additional diastolic high-pitched component.

(2) *Arch*

The diastolic part of the analogue curve may be normal, rejoining the zero line immediately after the "R" wave, or be partly or totally negative (positive on the spectral curve). The systolic part of the curve shows the same peculiarity as already described for the ascending aorta.

(3) *Aortic orifice*

The initial and final deflections are easily recorded as from normal subjects, but often have a greater amplitude with a sharper tone in the loudspeaker. There may be systolic dispersion of the dots on the spectrum as well as a diastolic dispersion often detected using a different orientation of the transducer (Fig. 10, right side).

(4) *Left ventricular outflow trace*

A broadening of the diastolic part of the spectrum was found at various sites in the left ventricular outflow tract close to the aortic valve or to the septum, or extending to the distal parts of the mitral valve.

SEVERE REGURGITATION (seven patients)

The diastolic part of the curve is entirely and deeply negative, as far downstream as the arch. The systolic wave shows indentations up to the arch;

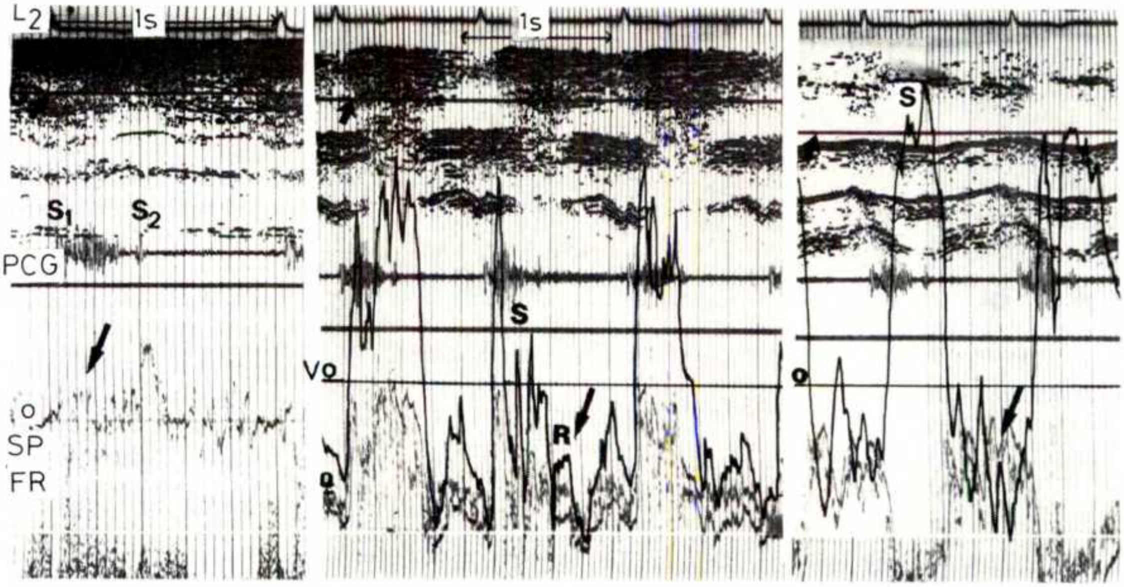


Fig. 9 *aortic orifice. Aortic flow velocity patterns in moderate stenosis associated with severe regurgitation (case 35 bicuspid calcified valve, same legend as Fig. 1 and 3A).*

Left: *aortic orifice. There is considerable dispersion of the dots in the spectral display (oblique arrow) indicating velocity disturbances; note the synchronous timing of the praecordial murmur on the phonocardiogram, with the dispersion of the dots on the spectral display. These disturbances are recorded only on intercostal space higher than the usual echo location of the transducer for examination of the aortic root and were only displayed with an asymmetrical location of the transducer disappearing when the centre of the aortic orifice was being sampled.*

Middle: *ascending aorta. Note the association of the characteristic abnormal systolic wave "S" with the negative wave throughout diastole ("R") (oblique arrow).*

Right: *aortic arch. The curve is delayed (delay of the Q-onset time interval equal to 0·05 s) and shows the same anomalies, though less pronounced in systole.*

the ejection time is sometimes prolonged. But the curve does not override the second sound and there is no significant time lag between the onset of the curves recorded at different levels of the aorta.

MODERATE REGURGITATION (seven patients)
The diastolic negativity is often important in the ascending aorta, but is much less obvious in the arch, though still present. The systolic wave shows a bifid pattern.

MILD REGURGITATION (three patients, and five additional externally diagnosed patients)
In all but three patients (case 13 and two non-invasively investigated patients), diastolic anomalies were elicited, consisting of negative phases of short duration, disappearing in the upper part of the ascending aorta, with a normal pattern at the arch. The systolic wave may be bifid or normal.

ASSOCIATED AORTIC STENOSIS AND REGURGITATION (Group 2C: 10 patients, Fig. 9)
Although not always present simultaneously, the analogue and spectral velocity curves show the same anomalies described in both the ascending aorta and arch for the separate lesions.

(1) *Moderate stenosis with mild regurgitation* (five patients)
The velocity curve shows systolic indentations in recordings made downstream from the aortic valve as far as the arch. The diastolic negativity disappears before the aortic arch is reached.

(2) *Moderate stenosis with moderate regurgitation* (three patients)
The same pattern is present for the systolic wave, but the diastolic negative flow velocity persists as far as the aortic arch though is less pronounced than in the ascending aorta.

(3) *Moderate stenosis with severe regurgitation* (one patient)
In a recording of the aortic arch, the systolic wave has the characteristic indentations with delay of onset of the curve and the diastolic part of the curve is conspicuously negative.

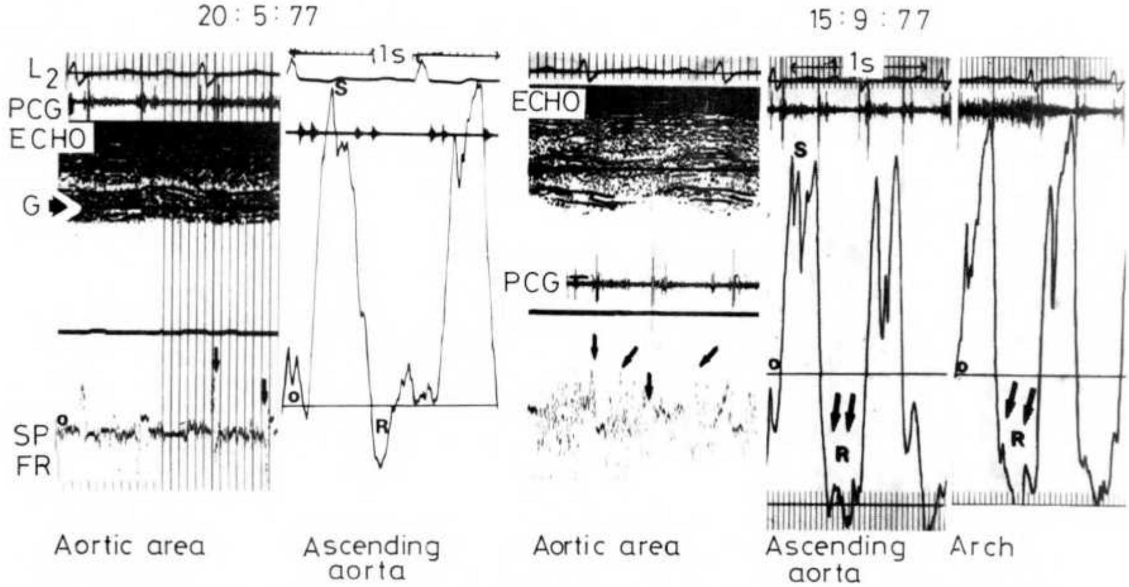


Fig. 10 *Aortic Björk prosthesis. Normal function (May 1977) (same legend as Fig. 3A and C). Praecordial recording of the velocity of prosthetic motion. The gate (G) is located at the level of the prosthesis and the record shows two very transient episodes of dot dispersion synchronous with the opening and closing of the prosthesis. There is also a narrow bandwidth of the spectrum in systole and diastole, indicating that there are no flow disturbances at the aortic orifice. The analogue flow velocity pattern is nearly normal and in the right-hand panel recorded several months later, the gate is located at the same position. Note the wide dispersion of the dots on the spectral display indicating velocity disturbances in systole and diastole. The analogue velocity curve also shows a bifid systolic pattern and pronounced diastolic negative flow indicating aortic regurgitation. At operation there was a paravalvular leak 1 cm² in area (case 25).*

(4) *Severe stenosis with mild regurgitation*
(one patient)

In this case there was a typical stenotic pattern of blood velocity in the ascending aorta as well as diastolic negative flow typical of regurgitation, but the evaluation of the stenosis was unreliable, a single recording only being available.

PATIENTS WITH AORTIC PROSTHESES
(Group 3: 13 patients, Fig. 10, left side)
(1) *Ascending aorta*

Transient dispersion of the dots is seen on the spectrum in more than half the cases. The corresponding analogue pattern is variable, being normal in four cases and bifid in two cases, with an indented "S" summit in seven cases. In four cases, slight diastolic negative velocity was present.

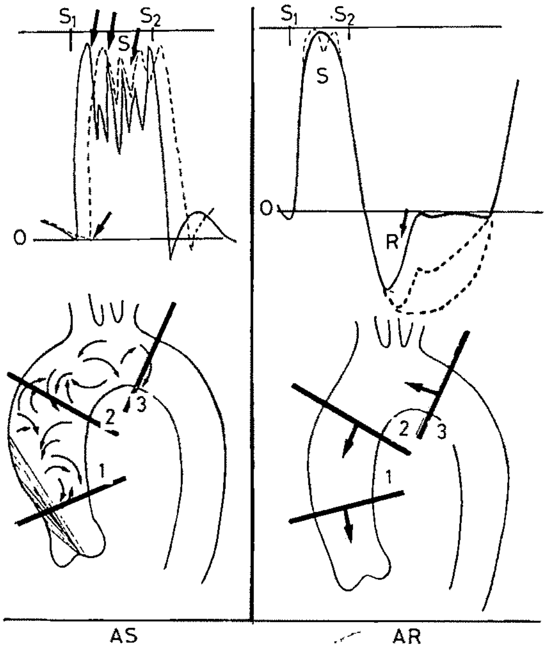


Fig. 11 *Schematic representation of the aortic flow velocity patterns in patients with aortic valve disease (grades 1, 2, and 3 correspond to mild, moderate, and severe lesion). AS, aortic stenosis; AR, aortic regurgitation; S1 and S2, first and second sounds.*
Left: *aortic stenosis. The typical indented systolic wave seen in the upper part may be recorded at various levels along the aorta, according to the severity of the lesion. The dotted curve represents the delayed velocity tracing recorded at the arch.*
Right: *aortic regurgitation. The depth and duration of the diastolic negativity of the velocity curve as well as the persistence of these anomalies lower down the aorta is related to the severity of the lesion.*

(2) *Arch*

The pattern shows some minimal disturbances of the spectrum and corresponding indentations on the summit of the S wave in the analogue curves (three patients). The Doppler loudspeaker signal is generally normal at the arch, and high-pitched but not prolonged in the ascending aorta.

(3) *Aortic orifice*

In all cases, two brief narrow deflections with opposite polarity were recorded, one at the beginning and the other at the end of systole. The respective polarities of the deflections were reversed using the suprasternal supraclavicular or thoracic approach. Between these two deflections, the velocity curve stayed close to the zero line. The loudspeaker signal had a sharp high-pitched tone.

CARDIAC PATIENTS WITHOUT AORTIC VALVE DISEASE (Group 4: 13 patients)

The anomalous summit pattern was found in two cases of pulmonary stenosis, one of them with Fallot's tetralogy. The other patients had normal systolic patterns in all aortic samples. A thin pattern with reduced systolic ejection time was found in one case of severe mitral regurgitation. In patients with atrial fibrillation the amplitude of the "S" summit varied depending on the previous diastolic interval. Where there was a long diastolic interval because of bradycardia or atrial fibrillation, the diastolic portion of the velocity curve may be irregular. In patients with Fallot's tetralogy, there was an obvious diastolic negativity owing to the presence of Blalock's anastomosis.

Aortic orifice

The findings were similar to those of the normal group except for the variable amplitude of the systolic deflections in patients with atrial fibrillation.

Discussion

Accurate diagnosis and evaluation of the severity of aortic valve disease by purely non-invasive methods has not so far been satisfactorily achieved. M-mode echocardiography as a rule provides no direct information about aortic valve lesions, but only indirect evidence based on its effect on left ventricular cavity size and wall thickness. Many uncertainties remain in assessing the severity of aortic valve disease and prosthetic valve function.[14] Cross-sectional echocardiography has the advantage of directly visualising the valve.[15] However, the accuracy of the diagnosis based on this technique remains to be demonstrated for all types of aortic valve disease. These problems emphasise the need for a more direct approach based on direct demonstration of the flow disturbances produced by the aortic valve disease.

Non-invasive measurement of blood flow velocity from the aorta using the suprasternal notch has been performed in the last decade using continuous wave Doppler equipment.[16–18] However, such methods are not useful in all types of disease and have emphasised the need for a more precise technique which can measure the velocity from a more limited sample of blood in the aorta. This has been met by the advent of pulse echo Doppler techniques introduced by Johnson *et al.* in 1973.[11] Several papers have been published describing pulse Doppler flow velocity measurements from the aorta[3 19] with or without echocardiography.[20] More recently, cross-sectional echocardiography has been combined with pulse Doppler techniques[21] but routine aortic velocity recordings could not be obtained. The method described here is based on velocity recordings from several different sites at various points downstream from the aortic valve, viz at the orifice in the ascending aorta, in the aortic arch, and in the proximal descending aorta. Diagnosis and assessment of the severity of the aortic valve lesions rely on pattern recognition and the timing of velocity events obtained from these curves. The main problems raised by the use of continuous wave Doppler blood velocity measurement have been discussed at length in previous publications.[22 23] It is pertinent to mention some technical limitations raised by the present equipment which is based on pulse echo Doppler, the time interval histogram, and zero-crossing rate meter. It is well known that the output of a zero-crossing meter, whether fed to an analogue velocity curve or a time interval histogram, is dependent upon the signal-to-noise ratio and upon the threshold setting. The time interval histogram has a gain setting which, if set too high, will cause broadening of the spectral display because of amplification of background noise. In the ATL system, the analogue velocity signal is the integrated average of the time interval histogram. Therefore, if there is a flow disturbance which has no net average velocity toward or away from the transducer, the analogue signal will sit at zero. In the examples where there is a net velocity, there will be a deflection from zero on the analogue velocity output and the time interval histogram will show spectral broadening displaced from the zero baseline. In the recordings obtained, care was taken to ensure the signals were not contaminated by noise by carefully adjusting the gain and sensitivity so that the recorded displays only showed true flow information. In order to achieve this, the gain was increased until the output was triggered by noise, then decreased until triggering was no longer observed.

The analogue signal is derived from the time interval histogram by passing it through integrating low pass filters. It therefore has an inherent delay depending upon the filter time constant. This time constant has been adjusted to produce minimal reproducible delays (0·03 s). Selection of the filter time constant is a matter of compromise between minimising this delay and producing a smooth curve. The influence of the angle theta between the ultrasound beam and the direction of blood flow is minimised when the suprasternal approach to the aorta is used since, from that location, the beam of ultrasound is nearly parallel to the direction of the central axis of the aorta.

Since none of these limitations of the technique limits its use for pattern recognition of abnormal velocity curves, discussion will be limited to the relation between the recorded curves and the pathological process producing the abnormal flow velocity.

VALIDITY AND SIGNIFICANCE OF RECORDED CURVES: DIAGNOSTIC VALUE

(A) *Normal subjects*

In normal subjects, the Doppler flow velocity patterns from the aorta are strikingly similar to those

Table 5 *Correlations between pulsed Doppler technique and classical procedures for diagnosing and assessing severity of aortic valvular lesions*

Diagnosis	*No.*	*Positive diagnosis*		*Sensitivity (%)*	*Specificity (%)*	*Correct evaluation of grading (%)*
		Classical procedures	*Echo pulsed Doppler*			
AS	16	Traumatic 11	10	90	87 pattern 100 pattern + timing	81
		Non-traumatic 5	4	87		
AR	22	Traumatic 17	16	94	88	82
		Non-traumatic 5	3	86	90	
AS + AR		Traumatic				
AS	10	10	9	90		77
AR			8	80		50

AS, aortic stenosis; AR, aortic regurgitation; "traumatic procedures" refer to haemodynamic, angiographic, and/or surgical findings.

of volume flow recorded using surgically implanted electromagnetic flowmeters in dogs and man,[24 25] or of flow velocity recorded experimentally and clinically using the pressure gradient technique,[26] the hot film anemometer,[27] and the electromagnetic flow velocity catheter probe during standard cardiac catheterisation.[28] The velocity curves therefore have the same physiological validity and significance.[29] Small positive diastolic oscillations are visible on some of our curves. Since a reflection wave is improbable at this level, they may be the result of diastolic wall displacements or artefact.

Effect of velocity profiles. The normal aortic velocity profile is almost flat except for a marginal region close to the arterial wall.[30–32] The recorded velocity pattern, whatever the site of recording, is therefore representative of the overall aortic flow velocity. However, the velocity curve is not directly related to volume flow since the aortic diameter may vary in diameter by a significant amount throughout the cardiac cycle.[33 34] Study of instantaneous flow velocity curves throughout the cardiac cycle demonstrates the physiological occurrence of flow disturbances during deceleration,[30] or present for a short time at the peak of ejection mainly in the ascending aorta.[27 35] These findings obtained with thin film anemometers agree with our observation of a slight broadening on the descending limb of the spectral curve and minute irregularities of the systolic summit. Our measured timing intervals are in general agreement with published reports for ejection time; the Q-onset interval of the velocity curve reflects the internal pre-ejection period taking into account the delay in the analogue velocity output.[36] No significant delay in onset of the systolic wave is found in normal subjects between the ascending aorta and the arch of the aorta.

Aortic orifice. The two deflections with coincident high-pitched signals on the loudspeaker are related to opening and closing movements of the aortic cusps whose echoes are simultaneously displayed on the echocardiogram, as previously noted by Johnson.[11] The deflections usually show the same positive sign, suggesting that they are generated by the motion of two different cusps. Nothing other than a brief early systolic disturbance can be recorded at this level in physiological flow.

(B) *Patients with aortic valve disease*

The velocity patterns recorded with the pulse echo Doppler in patients with aortic valve disease are also similar to those recorded using other techniques, both in experimental[37] and human studies; for instance hot film anemometer measurements in man with aortic stenosis,[30 35] electromagnetic flowmeter measurements at the time of surgery,[6 38] and electromagnetic catheter tip measurements in animals with artificially induced aortic regurgitation.[39] The externally recorded velocity curves therefore faithfully represent aortic flow velocity patterns and have the same pathophysiological significance as far as diagnosis and clinical applications are concerned.

The systolic broadening of the spectral display consequent on the dispersion of the dots on the time interval histogram probably reflects the irregular velocities of red blood cells present in turbulence generated by stenosis. The saw-toothed indentations seen on the analogue velocity curve may be considered a more obvious visualisation of the irregular character of turbulent flow velocities. The diastolic reverse flow velocity in aortic regurgition is the graphical representation of the reflux in the aorta. In these lesions, the peak velocity is not adequately represented whenever turbulent flow is present, either in the spectral or the analogue output and some artefacts may be present in the zero-crossing output because of its inherent non-linear properties.

Effect of velocity profiles. Instead of the nearly flat normal velocity profile, aortic stenosis is characterised by an irregular profile throughout the aortic cross-section, the highest velocities corresponding to the jet which is most commonly found near the anterior aortic wall.[30]

Effect of aortic diameter variation. The aortic cross-sectional diameter may vary by as much as 50 per cent during the cardiac cycle in cases of severe aortic regurgitation.[40] Consequently, the finding of a larger negative than positive velocity does not reflect the true volume flow in cases of gross regurgitation as previously stressed by Tunstall-Pedoe for the subclavian artery.[41]

AORTIC STENOSIS

(A) *Aortic velocity curves*

In 10 out of 11 patients, the characteristic abnormal systolic pattern was found, allowing a definite diagnosis to be established. This abnormality was also present in the patients with mild stenosis who were assessed purely by non-invasive procedures. The second striking feature seen in our recordings was the presence of different velocity patterns at the various sites along the aorta. The most abnormal velocity patterns were found in the samples close to the aortic orifice but they could persist for some distance downstream or be replaced by a normal or nearly normal pattern, either at the distal part of the ascending aorta or in the arch. The severity of the lesion, therefore, was not assessed purely on the existence of the abnormal "S" wave present in every stenosis, but on the persistence of the abnormality downstream from the valve. With this type of assessment, we could get a fairly good idea of the severity of the stenosis, comparable with the findings of invasive procedures (Table 6). This grading is in agreement with what we know of the propagation of turbulence downstream of a stenosed aortic valve.[30 35] In 45 per cent of the patients, the diastolic part of the curve was abnormal, exhibiting chaotic irregularities particularly when the recordings showed the maximum systolic disturbances. These findings may well be related to the diastolic persistence of turbulence previously shown in some individual cases.[30 35] The timing features are shown in Table 4. One significant anomaly was apparent when comparison was made with other groups of patients (Fig. 12).

There was a significant delay in the onset of the velocity curve when recorded from the aortic arch compared with that recorded from the ascending aorta, even in patients with mild aortic stenosis. This delay was also present in some samples recorded from the ascending aorta. It is not related to the left bundle-branch block seen in two cases since it is additional to the delay in the onset of the earliest velocity curve recorded near the aortic valve. The possibility of a technical fault cannot be excluded, though a possible distortion of the analogue curve was confidently ruled out by the simultaneous check with the spectral curve recording. Further studies will be required to elucidate this finding, which is peculiar to aortic stenosis in our study. It is consistent with the finding of Johnson *et al.*[11] who found later turbulence in the aorta than close to the aortic valve. Though some patients had extreme prolongation of the ejection time, the mean value did not reach a significant level ($p < 0{\cdot}02$) probably because of insufficient numbers of tracings, since these ejection times are severely abnormal when measured from pressure or carotid pulse traces.[42 43]

Table 6 *Correlations between left ventricular outflow tract turbulence detection and classical invasive procedures in pure aortic regurgitation (diagnosis and prognosis)*

Positive diagnosis			*Correct evaluation of grading* (%)
Classical procedures	*Echo pulsed Doppler velocimeter*		
	Sensitivity (%)	*Specificity* (%)	
17	94	80	70

Same abbreviations as in Table 5.

(B) *Aortic orifice examination*

Disturbance of the spectrum at the aortic valve is a useful sign of organic valve disease but is not specific for aortic stenosis and may be encountered with aortic regurgitation, especially when the cause is endocarditis with vegetations. Abnormality is not immediately evident in some cases and may be shown only by tilting the transducer from the optimal position for obtaining echo structure visualisation. Locating the disturbances with an eccentric location of the gate may be a useful clue to the presence of a biscuspid aortic valve (Fig. 8).

AORTIC REGURGITATION

(A) *Aortic velocity curves*

The velocity curves we recorded are comparable with the demonstration of aortic backflow in aortic regurgitation using angiographic techniques,[40] surgically implanted electric flowmeters,[6 38] and recordings from catheter-tip velocimeters.[39] The finding of negative diastolic velocity in the aortic flow pattern using pulsed Doppler appears to be a graphic representation of the regurgitant flow and confirms the diagnosis of aortic regurgitation. False positive results from the sample volume being placed close

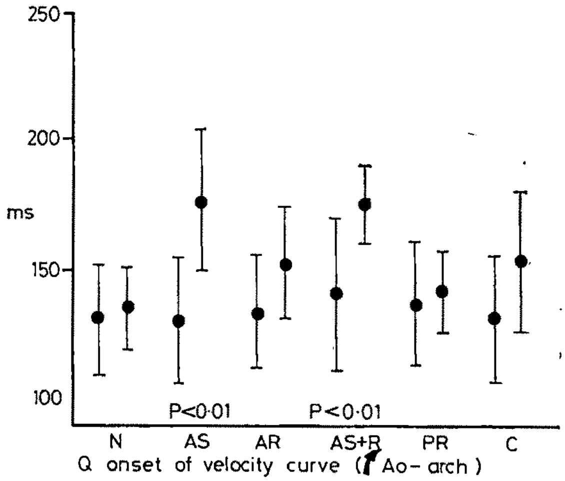


Fig. 12 *Comparative values of the Q-to-onset of the velocity curve time interval in the ascending aorta and in the arch (respectively, first and second vertical line for each group of subjects). ms, millisecond; N, normal subjects; AS, aortic stenosis; AR, aortic regurgitation; PR, patients with prosthesis; C, cardiac control group;* ● *mean value;* lower row, *the p values are indicated only when significant differences exist between the mean values. This diagram clearly shows the significant delay in the onset of the velocity curve at the aortic arch in patients with organic aortic stenosis.*

to the sinuses of Valsalva and recording discrete negative veolocities in diastole can be avoided by careful echocardiographic checking of the location of the sample volume. In view of the systolic changes in aortic diameter, it is clear that this qualitative method cannot be used to quantify the regurgitant flow and derive a regurgitant fraction. However, by using several different sample volumes at different sites in the aorta, it is possible to classify the regurgitation into three grades of severity. The possibility of either normal or disturbed systolic flow velocity which can be encountered in severe regurgitation[30] must be taken into consideration in assessing the severity of the lesion (Fig. 11).

Since there is no significant delay in the onset of the velocity curve at the arch in aortic regurgitation, this is a useful diagnostic criterion for distinguishing functional stenosis in severe aortic regurgitation from an organic valve stenosis, especially since the ejection time may be prolonged in both of these conditions. Very early onset of the systolic velocity curve may be noted in the ascending aorta in some cases where the end-diastolic ventricular and aortic pressures are almost equal. The insignificant delay in onset of the systolic curve compared with normal subjects could be a result of the frequent presence of aortic dilatation in aortic regurgitation.

(B) *Aortic valve orifice examination*

Systolic disturbances of the spectral display probably indicate functional stenosis though these were not always limited to early systole especially in patients with endocarditis. Diastolic turbulence is useful diagnostically but is less important in assessing prognosis.

AORTIC STENOSIS AND REGURGITATION

The velocity curves consistently showed anomalies characteristic of both stenosis and regurgitation though both anomalies were not evident on every sample. Sequential recordings along the aorta were required to confirm the diagnosis and make sure that one of the lesions was not being missed. The specific anomalies of timing were essential in assessing the presence of coincident aortic stenosis with significant aortic regurgitation.

AORTIC PROSTHESES

The study of these included two parts. (1) The recording of the velocity of opening and closing motion of the prosthetic valve: the amplitude and duration of these deflections were similar to those of normal aortic valves but were opposite in sign since they were related to the to-and-fro movement of a single element in the beam of the transducer. The polarity of the deflection varied according to the site of recording. No anomaly of these deflections was seen with a malfunctioning Starr-Edwards valve with paravalvular leak. Irregular amplitude of the deflections was noted with atrial fibrillation so this irregularity does not constitute by itself a sign of malfunction.

(2) Aortic velocity curve, with some spectral broadening in the time interval histogram and some saw-toothed indentations on the summit of the analogue velocity curve, is consistent with disturbed flow in the ascending aorta of patients with a prosthesis.[35] These patterns may be related to a pressure gradient across the prosthetic valve.[44 45] The absence of any timing abnormalities suggests the diagnosis of functional aortic stenosis. In diastole, the curve is similar to that of normal subjects except with a paravalvular leak when negative flow velocity was recorded as far distal as the aortic arch. These recordings led to the diagnosis of a paravalvular leak and, at operation, a paravalvular leak 1 cm^2 was found and repaired. It seems, therefore, that pulsed echo Doppler recordings may provide an additional method for assessing the function of valve prosthesis.

CONTROL GROUP

None of the characteristic abnormalities found in patients with aortic valve disease was encountered in this group. The curves were either identical to those found in normal subjects, or had a velocity pattern characteristic of the underlying condition, that is a systolic "S" wave of short duration in patients with severe mitral regurgitation, or traumatic ventricular septal defect or variable systolic amplitude in cases of atrial fibrillation with the amplitude of the "S" wave dependent on the preceding diastolic interval. There were minute negative diastolic oscillations where diastole was prolonged. However, in two cases of pulmonary stenosis, the "S" wave was indented but the normal timing of the velocity events ruled out aortic stenosis. These findings emphasise the importance of combining both pattern and timing informations. It seems likely that some aortic disturbances may occur in patients with pulmonary stenosis probably because of the proximity of the major vessels.[30]

Correlations with classical invasive procedures (Tables 5, 6)

PURE AORTIC STENOSIS

The Doppler method appears to be a useful diagnostic method, sensitivity and specificity being 87 to 90 per cent and reaching 100 per cent specificity when timing abnormalities were added to pattern recognition criteria. Assessment of the severity of the stenosis from the velocity curves was also reliable.

AORTIC REGURGITATION

The technique was equally valuable in the diagnosis and assessment of the severity of aortic regurgitation. Addition of the patients with mild regurgitation who had not been assessed invasively to the two groups hardly lessened the percentage of good correlations.

COMBINED STENOSIS AND REGURGITATION

The technique seemed to be equally valuable for diagnosis of patients with combined lesions. A correct evaluation of the grading of the stenosis was obtained in 77 per cent of cases, but there were some discrepancies in assessment of the severity of coincident aortic regurgitation, bringing the accuracy down to 50 per cent.

Discrepancies between Doppler assessment and invasive findings

DIAGNOSIS

False-negative diagnoses were exceptional and were made only in mild lesions (cases 10, 13, 30, 32, 38). They were all based on incomplete recordings. This underlines the critical need for a series of velocity samples to be obtained at different sites in the aorta for correct diagnosis. One false-positive diagnosis of aortic regurgitation resulted from placement of the sample volume close to the aortic wall. In the detection of turbulence, a high degree of sensitivity is preserved but specificity is less because of false-positive diagnoses in some cases of mitral regurgitation.

GRADING OF SEVERITY

Except for one case (case 36), discrepancies resulted from an overlap between grades. This was uncommon in pure lesions (cases 6, 27). In case 27, a low cardiac output might have led to erroneous underestimation. Though we have not experienced the same error with stenosis, the possibility must be borne in mind. The evaluation of combined lesions was satisfactory for the assessment of stenosis, with only two exceptions (cases 36, 38). Case 36 was the only one where there was a grading difference of 2: a tracing from a branch vessel was wrongly interpreted as an aortic arch recording. This mistake can be avoided by setting the sample volume at a suitable depth where it is unlikely to record from superficial vessels which do not always show the flow abnormalities. In combined lesions, assessment of aortic regurgitation by this technique was less satisfactory in this series, with four discrepancies (cases 29, 31, 36, 37). However, the differences involved only one grade.

Two of these discrepancies involved overestimation of the severity of the regurgitation. This probably resulted from measurements close to the jet from a stenotic valve where there may be large vortices with a negative component. To avoid this mistake we now record several samples close to each other in the same part of the aorta. In regurgitation the patterns are similar to each other and only alter progressively downstream, whereas with stenosis and its associated large vortices the pattern is chaotic. Where the results were discrepant, a low cardiac output has already been mentioned as a possible source of error and mitral valve lesions were often present in some cases. When aortic regurgitation is assessed purely on the detection of turbulence in the left ventricular outflow tract, the regurgitation may be wrongly estimated.

Limitations of method

Throughout this paper the technical limitations of the technique have been stressed. It is again emphasised that this is not a quantitative method of measuring flow or absolute velocity. From the clinical point of view, this is of minor importance since the diagnostic criteria are based purely on pattern recognition and timing abnormalities of the velocity curves. However, some rules have to be followed for accurate diagnoses using this technique. These include a careful echocardiographic check of the correct location of the Doppler sample, and the use of an adequate number of velocity samples which should be taken at a sufficient depth for the aortic samples to be well within the aorta. These velocity recordings are not always possible particularly in patients with emphysema. Rarely, in others, an adequate number of sites cannot be sampled for accurate assessment of the severity of the lesion, but, as a general rule, recording from the suprasternal notch is consistently successful. This is facilitated by the small size of the transducer. Deformity of the thoracic cage seems to be less of a drawback for this technique than for classical echocardiography. On the other hand, previous tracheotomy or presence of a tracheotomy tube makes the suprasternal approach extremely cumbersome.

Conclusions

Pulse echo Doppler blood velocity recordings need further technical improvements for a more complete demonstration of the complex flow disturbances generated in aortic valve disease. However, for purely clinical purposes, such as diagnosis and assessment of the severity of the lesion, this technique is very useful and reliable, and is useful also for the assessment of prosthetic valve function.

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Br Heart J 1980; **43**: 414–8

Diagnosis by ultrasound of severe carotid artery disease in patients undergoing cardiopulmonary bypass operations

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SUMMARY A non-invasive method using continuous wave Doppler shift ultrasound and spectral analysis was used as a screening test for severe carotid artery disease in patients undergoing cardiopulmonary bypass operations. One hundred and eighty-eight patients were examined before cardiac surgery (91 for ischaemic heart disease, 17 for ischaemic heart disease and valve replacement, 66 for valve replacement alone, and 14 for congenital abnormalities). The mean age of the 108 patients suffering from ischaemic heart disease was 54 years (±8) and that of the 80 patients admitted either for valve replacement alone or for congenital abnormalities was 52 years (±12). Five of the 108 patients suffering from ischaemic heart disease were found to have severe occlusive disease of the internal carotid artery by the ultrasound test, while the test was normal in the other two groups. Patients with severe carotid artery disease proceeded to carotid arteriography and endarterectomy before the planned heart operation.

Symptoms of cerebrovascular ischaemia are a well-recognised complication of open heart operations.[1–3] One explanation of such symptoms is that during surgery the blood pressure may be lowered on occasions to 40 mmHg or less and if severe occlusive carotid artery disease coexists this results in reduced cerebral perfusion.[4] This is likely to occur because occlusive arterial disease is often a generalised condition and both carotid and coronary arteries are favoured sites for the deposition of atheroma. The number of patients requiring open heart surgery is increasing, especially for treatment of ischaemic heart disease, and with the improvement in surgical techniques operations on older subjects are now undertaken.[2 5 6] There is, therefore, likely to be an associated increase in the incidence of postoperative complications resulting from carotid artery disease. Before this study was undertaken two patients in our department had recently died after operation without regaining consciousness despite no obvious complications occurring during cardiopulmonary bypass and necropsy showed severe, undiagnosed carotid artery disease in both cases.

Kartchner and McRae[7] have reported the value of oculoplethysmography for preoperative assessment of the carotid arteries in 216 patients undergoing operative procedures involving the heart, abdominal aorta, or arteries of the lower limb. Seventy-two patients were shown to have severe carotid artery disease, 35 of whom proceeded to carotid endarterectomy before the planned procedure and experienced no complications of cerebrovascular ischaemia from either operation. The remaining 37 patients in this group did not have a carotid endarterectomy and seven (19%) developed symptoms of cerebrovascular ischaemia after the planned operation.

Any non-invasive method used for assessing occlusive disease of the carotid arteries should identify those patients with a lesion severe enough to reduce distal mean pressure in the internal carotid artery. This paper is a report of our experience using Doppler shift ultrasound and spectral analysis[8 9] for this purpose in patients undergoing open heart surgery.

Subjects and methods

A total of 188 patients was assessed; 108 (94 men and 14 women) suffered from ischaemic heart

Received for publication 17 October 1979

disease and were admitted for aortocoronary bypass graft operations, and 80 patients (40 men and 40 women) required open heart surgery for valve replacement or congenital abnormalities. The mean age of the first group was 54 years (±8) and that of the other group 52 years (±12). Twenty-three had suffered from transient ischaemic attacks or had a localised carotid bruit, or both, as shown in Table 1.

The Doppler assessment was performed with the patient unsedated and lying supine on a couch. A Parks 805 blood velocimeter (10 MHz) was used to record Doppler shift signals from the supraorbital artery and the carotid bifurcation. This velocimeter was modified by the addition of a phase resolver[10] to permit simultaneous presentation of blood flowing towards and away from the transducer, thus providing information about the direction of blood flow in the insonated artery even in the presence of interference from venous signals. The transducer was placed on the skin overlying the artery of interest and backscattered signals from erythrocytes were immediately displayed by a spectral analyser[8] in sonogram form (Fig. 1).

The screening procedure consisted of insonating the supraorbital artery and observing the shape of the sonogram and direction of blood flow, both of which indicate whether disease is present.[9] The temporal artery occlusion test described by Brockenbrough[11] was modified[12] and used to detect lesions severe enough to cause a reduction in distal mean pressure in the internal carotid pathway. This test relies on the fact that normally there is equal pressure in the internal carotid and external carotid arteries. These two vessels usually form an anastomotic vascular bed in the region of the forehead via collateral vessels from the supraorbital and superficial temporal arteries, and in the normal situation there is a pressure gradient between the supraorbital artery and this collateral bed such that blood flows out of the orbit. If the pressure in the superficial temporal artery is reduced by digital compression there is a greater pressure gradient and erythrocyte velocities increase in the supraorbital artery (Fig. 2). However, if disease is present in the internal carotid artery sufficient to cause a reduction in distal mean pressure, blood flows into the orbit from the superficial temporal artery which is then at a higher pressure than the supraorbital artery. In this situation compression of the superficial temporal artery will usually stop or significantly reduce flow from the external carotid pathway into the supraorbital artery (Fig. 2). The presence of other collateral vessels may cause inaccurate results and we therefore compress other branches of the external carotid arteries both separately and simultaneously; these principally include the ipsilateral facial artery and contralateral superficial temporal and facial arteries.

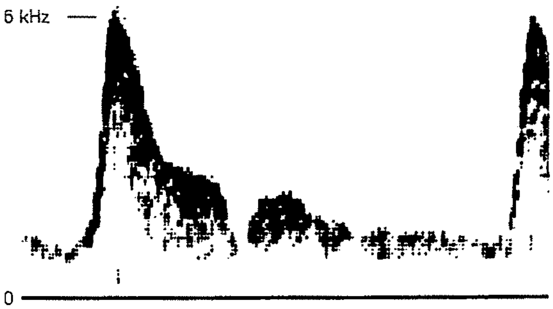

Fig. 1 *Normal sonogram from the common carotid artery over one cardiac cycle. Doppler shift frequency is on the Y-axis and time is on the X-axis. The blackness of the trace at any point is related to the number of erythrocytes generating the same Doppler shift (that is moving at the same velocity).*

The carotid bifurcation was then insonated, and when severe disease was present near the origin of the internal carotid artery high-velocity or turbulent Doppler shift signals[9] were usually obtained. The absence of a signal from the internal carotid artery indicated that this artery was totally occluded.

The presence of severe carotid artery disease shown by the non-invasive investigation was

Table 1 *Patients assessed using ultrasound for carotid artery disease before cardiopulmonary bypass surgery*

	Patients examined				
Operation	*No. of patients*	*Transient ischaemic attack (TIA)*	*Neck bruit transmitted from heart*	*Localised carotid bruit (LCB)*	*TIA and LCB*
Coronary artery bypass graft (CABG)	91	6	0	5	1
Valve replacement (VR)	66	9	22	0	0
CABG and VR	17	1	7	2	1
Congenital abnormality	14	0	4	0	0
Total	188	16	33	7	2

confirmed by carotid arteriography and an endarterectomy was performed six to eight weeks before open heart surgery.

Results

(1) ULTRASOUND SCREENING TEST

A summary of the 188 patients in this study is shown in Table 1, and in Table 2 are details of the five patients found to have severe internal carotid artery disease by the ultrasound examination. A diagnosis of bilateral severe disease was made in case 5, with complete occlusion of the left internal carotid artery.

(2) CAROTID ARTERIOGRAPHY

The ultrasound diagnosis was confirmed by carotid arteriography in four patients (cases 1 to 4). Total

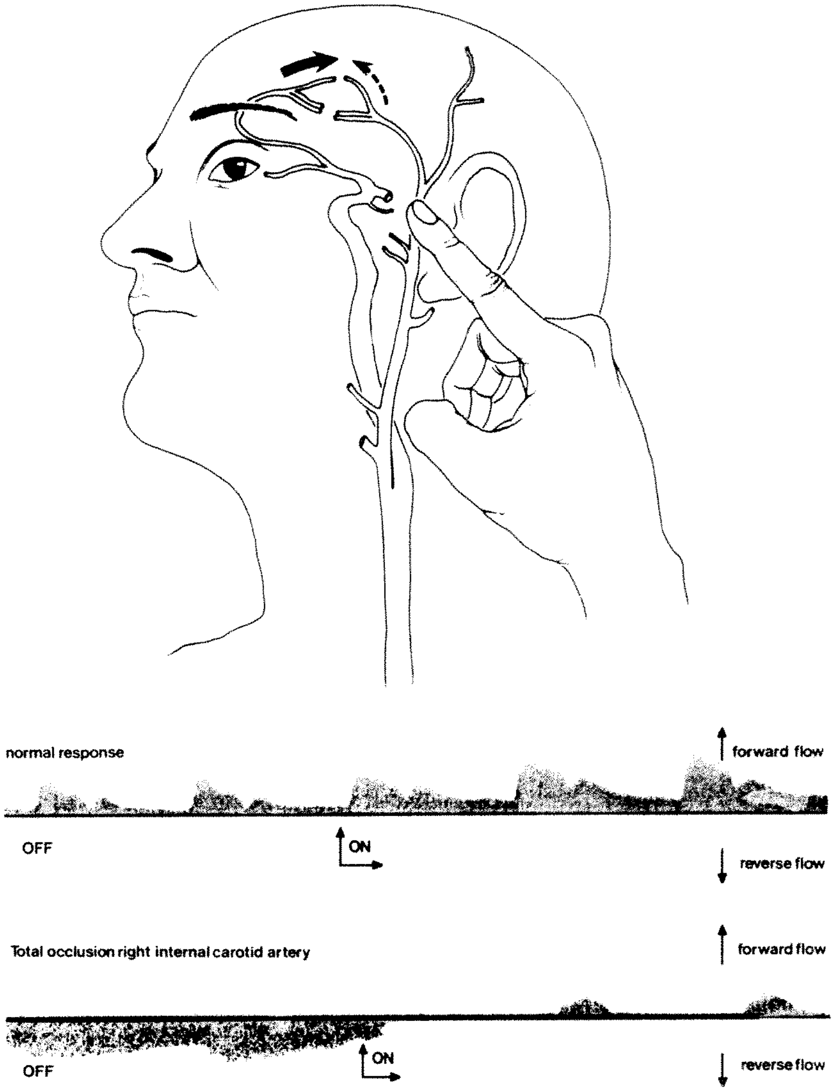

Fig. 2 Above: *Diagrammatic illustration of the anastomotic vascular bed between the internal and external carotid arteries in the forehead. The temporal artery occlusion test is performed by insonating the supraorbital artery and compressing the ipsilateral superficial temporal artery against the cranium.* Below: *Sonograms demonstrating a normal temporal artery occlusion test (top line) with augmentation of flow-velocities during compression. In an abnormal test (bottom line) blood flows initially into the orbit and is stopped by compression. In the case illustrated some blood then flows out of the orbit, indicating additional collateral supply to the internal carotid pathway.*

occlusion of the left internal carotid artery was confirmed in case 5, but on the right side the angiogram showed only minor lesions at both the origin and siphon of the internal carotid artery.

No complications occurred as a result of arteriography.

(3) SURGERY

Of the five carotid endarterectomies performed in patients shown to have severe disease by the ultrasound technique the only complication was in case 2 who had a left carotid endarterectomy and developed mild weakness of the right arm after the operation.

In case 5, though the right carotid arteriogram demonstrated only a 14 per cent reduction in lumen diameter, an endarterectomy was performed as the patient had had recent transient ischaemic attacks and the non-invasive investigation indicated that severe disease was present. This disagreement between the ultrasound and arteriogram result could have been partly explained by disease being present at more than one site, but may also have been a result of the *x*-ray image underestimating the size of the lesion at the origin of the internal carotid artery. This proved to be the case as at operation severe disease was found at the carotid bifurcation.

After open heart surgery one of the five patients died without regaining consciousness and necropsy disclosed a recent myocardial infarct. There were no cerebrovascular complications after cardiac surgery in the other patients who had had a carotid endarterectomy.

Discussion

An interesting finding in this study was that severe carotid artery disease was not found in patients who did not suffer from ischaemic heart disease, though the mean age of this group was similar to that of the group with the ischaemic heart disease. Five per cent of patients suffering from ischaemic heart disease were found to have severe occlusive lesions in the internal carotid artery. This finding accords with other reports that there is an association between the presence of occlusive arterial disease in the coronary and carotid arteries.[13 14] Though in this study carotid endarterectomy was undertaken some weeks before the heart operation, the two operations have been performed at the same time.[15 16]

This study confirms the limitations of relying on the presence of either a localised bruit in the neck or symptoms of cerebrovascular disease as indicators of severe occlusive disease of the carotid arteries.[9 17 18] A localised bruit was not present in three of the five patients with a severe internal carotid lesion (Table 2). In another patient one internal carotid artery was completely occluded but bilateral carotid bruits were present, and the fifth patient had only minor disease on the side of the bruit but severe disease on the contralateral side. The use of spectral analysis allows the examiner to know in which artery a bruit originates[19]; one patient with ischaemic heart disease who had not suffered from neurological symptoms had a localised carotid bruit and the ultrasound investigation demonstrated disease in the external carotid artery. Two patients with severe lesions in the internal carotid artery suffered from transient ischaemic attacks and only one of these had a carotid bruit associated with these symptoms. However, 14 other patients had also suffered from transient ischaemic attacks, and ultrasound showed no evidence of severe disease. Furthermore, two patients with severe internal carotid artery disease had no signs or symptoms of cerebrovascular disease.

In this study bilateral carotid arteriography was performed, but as confidence increases in the ultrasound diagnosis unilateral arteriography may be sufficient when ultrasound shows the presence of severe disease on one side only. An ultrasound vessel imaging system[20] is now being used for

Table 2 *Details of patients shown by ultrasound to have severe internal carotid disease*

Case no.	*Heart operation*	*Age (y)*	*Sex*	*Side with localised carotid bruit*	*Transient ischaemic attacks—carotid territory implicated*	*Side with severe disease diagnosed by ultrasound*	*Estimated reduction of lumen diameter on arteriograms of side with severe disease diagnosed by ultrasound*
1	Coronary artery bypass graft (CABG) and valve replacement	56	M	—	—	L	79%
2	CABG	57	F	—	L	L	52%
3	CABG	61	M	—	—	R	33%
4	CABG	51	M	R	—	L	83%
5	CABG	44	M	R and L	R and L	R and L	R, 14% L, 100%

further confirmation of the presence of disease at the carotid birfurcation, so that in cases of total occlusion of the internal carotid artery the non-invasive investigation may obviate the need for arteriography and allow precautions to be taken during open heart surgery.

Non-invasive assessment of the extracranial cerebral arteries using Doppler shift ultrasound and spectral analysis is a safe and relatively easy investigation to perform. It can be performed on an outpatient basis, has no contraindications, and the costs are approximately 10 per cent of those for arteriography. We suggest that this is a valuable preoperative investigation for all patients undergoing open heart surgery for ischaemic heart disease. However, the case for carotid endarterectomy as a treatment for both haemodynamically significant and minor carotid artery disease in these patients has still to be established in further studies.

We thank the British Heart Foundation for its financial support, and the Wellcome Trust, the Medical Research Council, and the Endowments Fund of Guy's Hospital for accompanying support. We acknowledge help from fellow members of Guy's Non-Invasive Angiology Research Group.

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Prescribing Information: Presentation Round, biconvex, scored, white tablets containing 2.5mg, 5mg or 10mg minoxidil. Tablets marked 2.5, 5 or 10 on plain side and U
on each side of score mark on other side. **Uses** Treatment of severe hypertension. Acts as a peripheral vasodilator and should be used with a diuretic and a beta-blocker.
Dosage and Administration *Adults* Dosage adjustments should be made at intervals of not less than 3 days, until optimal control of blood pressure is achieved. It
is seldom necessary to exceed 50mg per day. Dosage may first be increased to 10mg daily and subsequent increases should be by increments of 10mg in the daily dose.
Children For patients of 12 years of age or below, dose at 0.2mg/kg with increments of 0.1mg-0.2mg/kg in daily dose at minimum of 3-day intervals. Maximum
recommended dose is 1.0mg/kg daily. **Rapid reduction of blood pressure** Rapid reduction of blood pressure can be achieved using continuous blood pressure
monitoring and incremental doses of 5mg every 6 hours. Loniten therapy should always be accompanied by diuretic and beta-blocker treatment (See Data Sheet).
Contra-indications, warnings etc *Contra-indications* Phaeochromocytoma. *Warnings* If used alone, Loniten can cause a significant retention of salt and water leading
to positive physical signs such as oedema, and to clinical deterioration of some patients with heart failure. Diuretic treatment alone, or in combination with restricted
salt intake is, therefore, necessary for all patients taking Loniten. Patients who have had a myocardial infarction should only be treated with Loniten after a stable post-
infarction state has been established. The physican should bear in mind that if not controlled by sympathetic suppressants, the rise in cardiac rate and output that
follows the use of potent vasodilators may induce anginal symptoms in patients with undiagnosed coronary artery disease, or may aggravate pre-existing angina
pectoris. The effect of Loniten may be additive to concurrent antihypertensive agents. The interaction of Loniten with sympathetic blocking agents such as
guanethidine or bethanidine may produce excessive blood pressure reduction and/or orthostasis. *Precautions* The safety of Loniten in pregnancy remains to be
established. Hypertrichosis occurs in most patients treated with Loniten and all patients should be warned of this possibility before starting therapy. Spontaneous
reversal to the pre-treatment state can be expected 1-3 months after cessation of therapy. Soon after starting Loniten therapy approximately 60 per cent of patients
exhibit E.C.G. alterations in the direction and magnitude of their T waves. Large changes may encroach on the ST Segment, unaccompanied by evidence of ischaemia.
These asymptomatic changes usually disappear with continuing Loniten treatment. The E.C.G. reverts to the pre-treatment state if Loniten is discontinued. Pericardial
effusion has been detected in patients treated with a Loniten-containing regime. A cause and effect relationship has not been established. Most effusions have either
been present before Loniten was given, or occurred among uraemic patients. However, it is suggested that Loniten-treated patients should be periodically monitored
for signs or symptoms of pericardial effusion and appropriate therapy instituted if necessary. Salt and water retention in excess of 2 to 3 pounds may diminish the
effectiveness of Loniten. Patients should, therefore, be carefully instructed about compliance with diuretic therapy and a detailed record of body weight should be
maintained. *Side-Effects* Most patients receiving Loniten experience a diminution of pre-existing side effects attributable to their disease or previous therapy. New
events or side effects likely to increase include peripheral oedema, associated with or independent of weight gain; increases in heart rate; hypertrichosis; and a
temporary rise in creatinine and blood urea nitrogen. Gastrointestinal intolerance, rash and breast tenderness are infrequently reported side effects of Loniten
therapy. **Pharmaceutical Precautions** None. **Legal Category** POM. **Package Quantities** 2.5mg, 5mg and 10mg Loniten tablets supplied as bottles of 100. **Basic NHS
Cost (UK)** 2.5mg – £4.50. 5mg – £8.00. 10mg – £15.50. Data Sheet available on request.

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Br Heart J 1980; **43**: 419–25

Effects of beta blockade on work—ΔST segment curves during exercise, and relation to subsequent results of coronary artery bypass surgery

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SUMMARY In 44 patients with coronary disease the relation between work and ST segment depression (ΔST) was investigated during graded exercise standardised in terms of each subject's maximum work capacity (W max). In 10 patients who were subsequently treated medically (group M) the relation remained unaltered during subsequent studies at three and 12 months.

In all patients the effect of beta blockade (3 mg pindolol iv) on the work–ΔST relation was examined and two groups were identified before surgery on the basis of their response to the beta blocker. In 28 patients who subsequently underwent coronary bypass surgery (group S_A) and the 10 patients of group M beta blockade significantly altered the relation so that there was less ST depression at a given workload. However, in six patients who also subsequently underwent bypass surgery (group S_B) there was paradoxically more pronounced ST depression after pindolol. There was no alteration in maximum work capacity after pindolol in any of the groups.

In the 28 group S_A patients there was one death after surgery; the work–ΔST relation in the other 27 patients of this group was even less depressed than with pindolol at a given workload and maximum work capacity had increased by 32±6 per cent; most patients were asymptomatic. In group S_B patients the response to surgery was uniformly poor and all patients continued to have angina. No change occurred in the work–ΔST relation after surgery, there were two late deaths, and all six patients had evidence of postoperative infarction.

The direction of shift by beta blockade of work–ΔST curve may have prognostic significance for subsequent coronary artery surgery.

There have been relatively few studies in which medical and surgical treatment for ischaemic heart disease have been compared in the same patients using objective methods.[1] While factors such as left ventricular dysfunction or distal coronary artery disease have been identified as important determinants of outcome after coronary artery bypass grafting, the identification by other criteria of subgroups with a good or poor prognosis remains an important priority.

In the present study, changes in maximum work capacity and the relation between work and ST segment depression (ΔST) were examined in 44 patients with ischaemic heart disease, before and after acute beta blockade. The effects of beta blockade were compared in 34 patients with those of coronary artery surgery and after long-term medical treatment in the remainder. A group was identified before surgery in whom there was a paradoxical response to acute beta blockade and in whom most of the subsequent postoperative morbidity and mortality occurred.

Received for publication 6 September 1979

Method

Forty-four patients with severe chronic stable angina under consideration for coronary artery bypass grafting were admitted to the study which was performed with the approval of the Alfred Hospital Ethics Committee.

Cardiac catheterisation with left ventricular angiography and coronary arteriography was performed within one to two days of the initial exercise test (see below). Selection for subsequent treatment was then made. Selection for medical treatment (10 subjects) (group M) was either because of mild symptoms (four patients) or distal coronary artery disease (six patients). Surgery was advised in 34 patients (group S). This was usually because of severe angina in the presence of proximal coronary artery disease and good left ventricular function assessed from angiographic findings. The findings are given in Table 1.

After surgery or the institution of medical treatment patients were managed by their own doctors, and exercise tests were repeated in all patients after three and 12 months and in most after two years. Clinical, electrocardiographic, haemodynamic, and angiographic findings were classified according to the definitions of the American Heart Association.[2] Angina was classified as being either absent, mild if it occurred only on strenous exertion, moderate if it occurred during the patient's normal daily activities, and severe if it occurred at rest or on very mild exertion.

EXERCISE TESTS

Graded exercise testing was performed using the procedure previously described by Bailey *et al.*[3] The patients had previously become familiar with the exercise procedure and had ceased all medication except glyceryl trinitrate at least one week before each test. The meal immediately preceding the test was omitted. Exercise was performed on an Elema-Schonander bicycle ergometer with electrocardiographic monitoring using an Avionics Exerstress 3000 recorder. ST segment depression (ΔST) was measured by the shift in ST segment from the baseline established in the PR interval, 70 milliseconds from the end of QRS complex. Heart rate and ST were averaged over 15 beats for three consecutive 15 beat periods at the end of each workload. Blood pressure was recorded by sphygmomanometry using a microphone situated over the brachial artery.

After a two-minute warm up period with no load on the bicycle ergometer, a 'sprint' test was performed with work progressively increased by 100 kpm each minute until symptoms prevented a further increase in workload. The workload at which this occurred was designated as maximum work capacity (W max). If a given workload was not completed the time was rounded off to the nearest 30 seconds and maximum work capacity expressed to the nearest 50 kpm/min. Before treatment the reason for stopping exercise in all patients was typical angina pectoris. In some patients this was associated with breathlessness, calf pain, or leg fatigue, but these symptoms were not dominant.

Displacement of the ST segment was measured at each level of exercise and the result plotted against workload. The results for a typical patient are shown in Fig. 1. For presentation of group work–ΔST relation (for example Fig. 2, 3) work in kpm/min has been normalised in terms of the W max for each test to allow for the variation in maximum workload achieved by different subjects.[3] Since no change occurred in W max after acute beta blockade normalisation in this way has no effect on the work–ΔST curves after pindolol though the increase in W max in some patients after surgery tends to exaggerate slightly the change in ST segment after surgery when work is normalised.

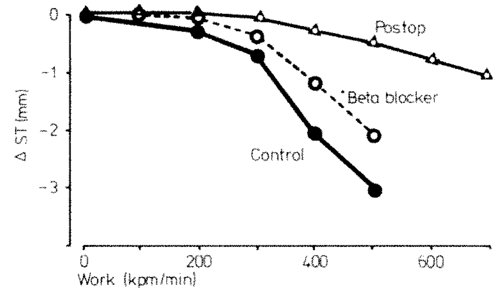

Fig. 1 *Relation between work (kpm/min) and ST segment depression in a typical group* S_A *patient before surgery (control), after 3 mg iv pindolol (beta blocker), and three months after coronary artery bypass grafting (postop).*

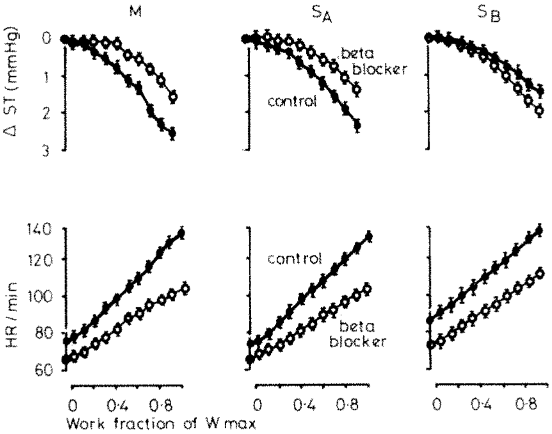

Fig. 2 *The relation between work normalised as a fraction of each patient's maximum work capacity and ST segment displacement* (top half), *and with heart rate* (lower half) *before and after 3 mg iv pindolol. HR, heart rate; M, medically treated group ($n=10$);* S_A*, surgically treated group with a favourable ST response to beta blocker ($n=28$);* S_B*, surgically treated group with an unfavourable response to beta blocker ($n=6$); W max, maximum work capacity.*

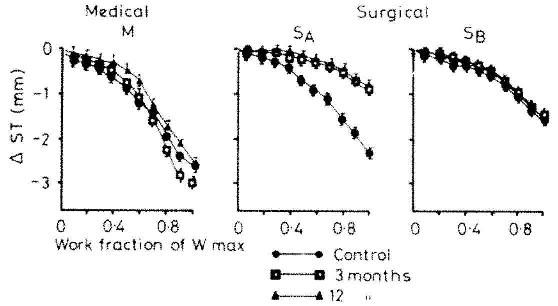

Fig. 3 *Relation between normalised work and ST segment displacement in each of the three groups before treatment (control), and three months and 12 months later. M, medically treated group (n = 10); S_A, surgically treated group with a favourable ST response to beta blocker (n = 28); S_B, surgically treated group with an unfavourable response to beta blocker (n = 6); W max, maximum work capacity.*

Ten minutes after the completion of the test pindolol 3 mg was administered intravenously over three minutes. The 'sprint' exercise test was then repeated after 45 minutes. Venous blood, 10 ml, was collected at the end of the second test for subsequent assay of plasma pindolol by the method of Pacha.[4]

CARDIAC CATHETERISATION AND ANGIOGRAPHY

Percutaneous femoral techniques were used. Injections for the left ventricular angiograms were in the right anterior oblique position and multiple projections were used for the coronary angiograms. Left ventricular dysfunction was classified as local if the abnormality was confined to one or two adjacent segments (defined by the American Heart Association[2]) or generalised if three or more segments were involved. Ejection fraction was greater than 35 per cent in all patients.

CORONARY ARTERY BYPASS GRAFTING

Coronary artery bypass grafting was performed by four different surgeons using aortocoronary saphenous vein grafts. Techniques varied slightly among surgeons, but in general all vessels found to have significant disease were grafted if possible. In three patients endarterectomy was performed on the right coronary artery before a graft was inserted. In one patient a small apical aneurysm was plicated at surgery. After operation electrocardiograms, serum aspartate transaminase (AST), lactic dehydrogenase (LDH), and creatinine kinase (CK) measurements were performed daily for at least five days. Technetium scans and CK MB isoenzyme measurements were also performed in some patients if the diagnosis of perioperative infarction was suspected.

MEDICAL TREATMENT

Group M (medically treated) were managed by their own physicians who prescribed beta-blocking drugs to most patients (Table 3).

STATISTICAL METHODS

Work–ΔST relations were analysed using standard methods of regression analysis as described by Snedecor and Cochran.[5] Other data were analysed by analysis of variance or paired t tests. Results are expressed as mean ± standard error of the difference caused by variation within subjects derived from the analysis of variance.[5]

Results

WORK–ΔST CURVES

The relation between work, normalised as a fraction of each patient's maximum work capacity, and ΔST was found to be curvilinear in all patients before treatment (Fig. 2). After administration of pindolol the relation altered in 38 patients so that less ST segment depression occurred for a given workload ($p < 0{\cdot}01$). Ten of these patients were treated medically (group M). Operation was performed in 34 patients (group S). In 28 of these patients the shift from control after beta blockade was similar to that in group M (group S_A). However, in six patients there was a shift in the opposite direction after beta blockade in the work–ΔST relation so that there was more ST depression at a given workload above 0·5 maximum work capacity (group S_B) ($p < 0{\cdot}01$). Each of these patients subsequently underwent surgery. The clinical characteristics of the three groups of patients are summarised in Table 1.

At three and 12 months (Fig. 3) the work–ΔST curves obtained without beta blockade in group M remained virtually unaltered from the control response. However, at three months the surgically treated patients who had responded favourably to acute beta blockade now had significantly less ST segment depression for a given workload (groups S_A) ($p < 0{\cdot}01$). By contrast, for the surgical patients with the previous paradoxical response to pindolol the work–ΔST segment relation remained the same as before surgery. There was no further change in this relation in any of the groups after 12 months. Thus one year after entry into the study, only the patients in group S_A showed improvement in the work–ΔST relation. Not all patients reported for their exercise tests after two years though clinical information was obtained from all surgically treated patients. In 18 group S_A patients and three group S_B patients no significant change occurred in the work–ΔST relation between one and two years after operation.

MAXIMUM WORK CAPACITY

Maximum work capacity before treatment was 900 ±82, 677 ±33, and 658 ±55 kpm/min for groups M, S_A, and S_B, respectively (Fig. 4). The higher value for group M reflected the greater heterogeneity of the extent of disease of patients in this group. No change occurred in any group after acute beta blockade. After three and 12 months of medical treatment mean maximum work capacity in group M patients was 867 ±110 kpm/min, not significantly different from control. However, three months after surgery maximum work capacity in group S_A patients had increased on average by 19·3 ±6 per cent to 808 ±34 kpm/min ($p < 0{\cdot}001$) and this figure was still maintained 12 months after operation and was then 860 ±36 kpm/min. However, in three of the five patients in group S_B who were still alive three months after operation, maximum work capacity had not increased from the preoperative value.

Table 1 *Clinical characteristics at entry*

	Medical	*Surgical*	
Group	*M*	S_A	S_B
Number of patients	10	28	6
Age (y)	43·3 ±5 (range 32 to 62)	53·4 ±1·3 (range 38 to 62)	47·7 ±3·6 (range 39 to 62)
Past history			
Myocardial infarction	4	18	4
Unstable angina	2	3	1
Cardiac failure	2	4	0
Resting electrocardiogram			
Infarct	3	15	4
Haemodynamics			
LVSP (mmHg)	136 ±5	130 ±3·2	142·8 ±7·8
LVEDP (mmHg)	14 ±1·1	13·0 ±1	13·8 ±1·9
Cardiac index (l/min per m^2)	3·1 ±0·15	3·0 ±0·15	2·9 ±0·29
LV angiogram			
Normal	5	13	3
Local dysfunction	3	12	2
Generalised dysfunction	2	3	1
Coronary angiograms			
One vessel diseased	2	2	0
Two vessels diseased	5	8	1
Three vessels diseased	3	18	5

LVSP, left ventricular pressure; LVEDP, left ventricular diastolic pressure.

HEART RATE CHANGES AND PLASMA PINDOLOL

There was a linear relation between heart rate and workload in all patients (Fig. 2). Maximum heart rates attained by the three groups were similar at 136 ±4·3, 133·6 ±1·7, and 133·8 ±2·4 beats/min for groups M, S_A, and S_B, respectively. After pindolol the rise in heart rate for increasing work was attenuated similarly in each group so that overall the slope of the work-heart rate relation was reduced by 31·7 per cent ($p < 0{\cdot}001$). At three months maximum heart rates attained were similar to control in group M, but significantly higher in the post-surgery patients at 142·5 ±2·7 beats/min, the increase being in proportion to their increase in maximum workload.

Mean plasma pindolol concentrations 45 minutes after administration were 39·6 ±8·7, 43·2 ±6·7, and 42·6 ±5·7 ng/ml for groups M, S_A, and S_B, respectively.

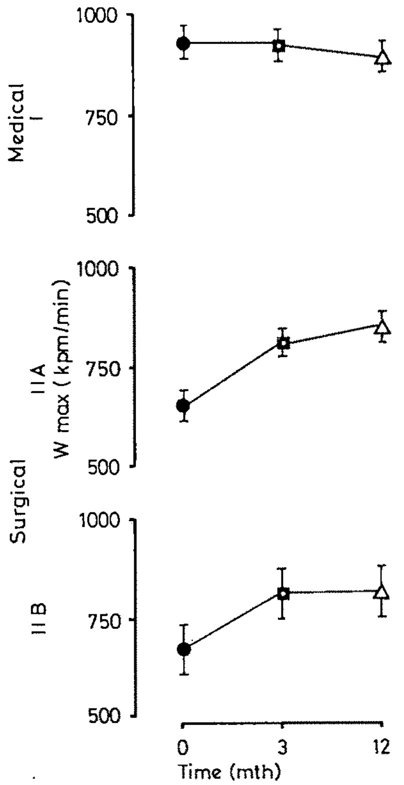

Fig. 4 *Maximum work capacity in groups M, S_A, and S_B before treatment at three months and 12 months. W max, maximum work capacity.*

MORBIDITY AND MORTALITY

Medical patients

Before coronary angiography each patient had either moderate or severe angina. In group M patients severity of angina was similar at each time period when they were taken off medical treatment. Two years after coronary angiography all 10 group M patients were alive, with symptoms unchanged from those at entry to the study.

SURGICAL PATIENTS

All patients had moderate or severe angina before surgery. The average number of grafts performed in each was 2·48 in group S_A and 2·67 in group S_B. The incidence of myocardial infarction after operation is shown in Table 2. All six patients in group S_B developed electrocardiographic evidence of myocardial infarction within the first two years after operation and in five of these the evidence was definite with typical electrocardiographic abnormalities as well as a diagnostic rise in myocardial enzymes.

Clinical response to surgery varied considerably between the two groups. In group S_A, one patient died suddenly three months after operation. In group S_B, one patient died in the perioperative period after a large myocardial infarct and another died suddenly 18 months after operation. Of the surviving patients, 25 in group S_A (93%) were completely without anginal symptoms three months after operation and 23 (82%) at two years. All four patients in group S_B were experiencing typical angina pectoris of moderate or severe degree two years after operation. The symptoms in these patients are reflected in the drugs prescribed by their physicians (Table 3). Beta blockers had been stopped one year after operation in 23 patients in group S_A and in only one patient in group S_B ($p < 0{\cdot}005$).

Discussion

The morbidity and mortality of the whole group of surgically treated patients are similar to those recently reported.[1] The effects of beta blockade and of surgery on maximum work capacity and ST changes during exercise are also in agreement with previous findings,[6–9] though, to our knowledge, the effects of beta blockers and surgery have been examined in the same patients in only one study.[6] However, using the change in work–ΔST curve after beta blockade a subgroup was identified in this study in whom there was subsequently a much higher incidence of patients with persistent angina, myocardial infarction, and death after surgery.

The present study has shown that the relation between standardised work and ST segment depression is curvilinear in patients with angina resulting from coronary artery disease, in agreement with previous findings.[3] The results of repeated tests over a period of one year in patients of group M in whom the degree of angina did not change shows that the relation is reproducible, as is the value of maximum work capacity, Thus, the fact that in the surgically treated patients of group S_A there was less ST depression for a given standardised workload as well as a significant rise in absolute value of maximum work capacity and maximum heart rates during exercise suggests diminution in the degree of myocardial ischaemia and improvement in myocardial function despite presumed increase in oxygen demand. The value of maximum work capacity in group S_A after surgery of 860 kpm is approaching the normal range for a middle-aged Australian population.[10] Improvement in exercise performance after coronary surgery has been noted in patients in whom no grafts are patent, possibly related to myocardial infarction at the time of surgery.[11] It is unlikely that this is the cause of

Table 2 *Postoperative myocardial infarction*

	S_A	S_B
Number of patients	28	6
In hospital		
No evidence	24	2
Enzymes only	2	1
New Q waves only	0	1
New Q waves and enzymes	1*	2
New Q waves, enzymes, and scan	1	1
	4	5
Late		
New Q waves and enzymes	0	2
Total possible postoperative infarction	4	6

*Normal scan.

Table 3 *Drug treatment*

	M	S_A	S_B
Digoxin			
Entry	3	9	1
3 months	2	6	2
12 months	2	2	2
Beta blockers			
Entry	8	24	4
3 months	8	2	3
12 months	8	1	3
No drugs			
Entry	1	4	2
3 months	0	17	2
12 months	0	22	2

the improved exercise performance in many patients in group S_A, as the graft patency rate around the time of the present study in this centre was 93 per cent in 63 consecutive patients who had 172 grafts (unpublished data). By contrast, group S_B patients showed no improvement in work–ΔST relation, despite having the least initial ST depression of the three groups, nor any improvement in maximum work capacity or maximum heart rate during exercise. Presumably, any improvement resulting from myocardial revascularisation was cancelled out by the clearly complicated postoperative course followed by these patients.

It is of interest that by standard clinical and haemodynamic criteria this latter group was considered suitable for bypass grafting and was indistinguishable from group S_A. The only retrospective difference between the two surgical groups was the response to acute beta blockade during the initial exercise test.

The attenuation, without complete restoration to normality in groups M and S_A observed in the standardised work–ΔST segment relation after pindolol, was similar to that observed previously after other beta blockers.[3 12] Beta blockade did not alter maximum work capacity, but lowered the heart rate at a given workload. The dose of pindolol produces maximum beta blockade of the heart rate response to exercise in normal subjects under conditions similar to those of the present tests.[13] The plasma pindolol concentrations of 25 to 35 mg/ml of the present study are on the upper plateau of the concentration-exercise heart rate response curve. Hence the reduction in ST depression at a given workload in groups M and S_A suggests diminution of myocardial ischaemia resulting from a reduction in myocardial oxygen demand, secondary to the attenuated heart rate response. However, in group S_B the degree of myocardial ischaemia is apparently aggravated at high workloads despite the fact that the heart rate response was attenuated to a similar degree to that in group S_A. The reason for the aggravation of ischaemia is not apparent from the present study, nor can it be determined whether similar results would occur after other beta-blocking drugs with somewhat different properties. It is likely, however, that the results would apply to other drugs in view of the results of studies showing approximately equal effectiveness in angina of noncardioselective and cardioselective agents and drugs with intrinsic sympathomimetic activity.[14] A likely reason for deterioration after acute beta blockade is an increase in myocardial oxygen demand caused by an increase of ventricular dimensions associated with cardiac slowing.[15]

In group M and group S_A patients the increase in oxygen demand resulting from this factor is apparently more than balanced by the reduced demand caused by lowering of heart rate and arterial pressure. It seems likely that in group S_B patients acute beta blockade unmasks serious left ventricular dysfunction that has been masked by sympathetically mediated support of myocardial function. Such unmasking of ventricular dysfunction with propranolol has been previously observed in the open chest dog model of myocardial ischaemia.[16]

Some patients with angina caused by coronary artery spasm show a deterioration after beta blockade.[17] None of the patients in group S_B were noted to have coronary artery spasm during their coronary arteriogram, nor to have ST elevation, and it seems unlikely that this accounted for the response to acute beta blockade in these patients.

The present study suggested that using objective testing with work–ΔST curves a subgroup can be identified characterised by a paradoxical increase in ischaemia after acute beta blockade. Since inadequate clinical therapeutic response to beta blockers is an accepted indication for coronary artery surgery, distinction should be drawn between patients with an inadequate response to beta blocker, and those with a paradoxical result during the diagnostic test. The retrospective correlation between poor surgical results and the initial response to beta blockade warrants further investigations, as does the prognosis of such patients when treated medically.

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Br Heart J 1980; **43:** 426–35

Thallium-201 exercise myocardial imaging to evaluate myocardial perfusion after coronary artery bypass surgery*

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SUMMARY To assess the usefulness of thallium-201 exercise scintigraphy in evaluating myocardial perfusion after coronary artery bypass surgery imaging was performed after submaximal bicycle ergometry and at rest in 54 patients before and within 24±10 (SD) weeks after operation. According to the postoperative scintigram the patients were assigned to three groups. Group 1 comprised 31 patients whose perfusion returned to normal after exercise and at rest within the preoperatively ischaemic regions; group 2 comprised 16 patients with identical pre- and postoperative exercise-induced perfusion defects, and group 3 comprised seven patients with enlarged or new perfusion defects postoperatively.

Clinically, 14 of 31 patients in group 1 were symptom free after operation, two of whom, however, showed an abnormal exercise electrocardiogram; whereas the other 17 patients still complained of chest pain and in six of them the exercise electrocardiogram was also pathological. In group 2 eight of 16 patients were symptom free after operation and showed normal exercise electrocardiograms and the other eight continued to suffer from angina, and seven had a pathological exercise electrocardiogram. All seven patients in group 3 were symptomatic and showed an abnormal exercise electrocardiogram. Thus, scintigraphy identified eight of 20 patients (40%) who were symptom free and showed normal exercise electrocardiograms as still having exercise-induced ischaemia and thus as having not truly benefited from the surgical intervention. In contrast, improvement in perfusion was documented in 17 of 31 patients (53%) despite further complaints of chest pain and persistence of a pathological exercise electrocardiogram in six of them.

Bypass graft patency rate paralleled the scintigraphic findings in the 35 patients who were restudied arteriographically. In group 1 (16 patients restudied) the graft patency rate was 81 per cent, significantly different from the 38 per cent in group 2 (13 patients restudied), and it was only 15 per cent in group 3 (six patients restudied). Similarly, the degree of vascular obstruction had decreased in group 1 from a score of 2·1±0·3 (SEM) preoperatively to a score of 1·1±0·3 postoperatively, remained unchanged in group 2, averaging 3·0±0·4 score values preoperatively and 3·1±0·5 score values postoperatively, and even tended to increase in group 3 from 2·2±0·6 score values preoperatively to 3·3±0·6 score values postoperatively.

It is concluded that thallium-201 exercise scintigraphy is a useful technique to document changes in regional perfusion after surgery and is definitely superior to the clinical evaluation of patients including the exercise electrocardiogram.

More than 10 years have elapsed since coronary artery bypass surgery was introduced into the management of coronary heart disease as a new therapeutic principle. Because of the low operative mortality and the high incidence of symptomatic improvement, the technique has recently become one of the most popular surgical procedures in the United States and Western Europe.[1–3] Relief of

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*This work was supported partly by a grant of the Fritz Hoffmann-La Roche Foundation for Medical Research.

Presented in part at the First Joint Meeting of the Working Groups of the European Society of Cardiology, Brighton, UK, 1978.

Received for publication 29 August 1979

pain is generally attributed to successful revascularisation and usually correlates with graft patency. Several patients, however, have benefited symptomatically despite angiographically verified graft closure.[4–6] Moreover, with regard to angina pectoris perioperative myocardial infarction could conceal unsuccessful coronary revascularisation.[7 8] On the other hand, there are patients with patent grafts who describe postoperative chest pain often indistinguishable from true ischaemic angina.

Since the success or the failure of surgical revascularisation is not always apparent clinically or from routine laboratory tests such as the exercise electrocardiogram and the determination of the physical working capacity, other techniques which provide a more specific picture of the postoperative status of vascularisation are needed. The morphological proof of bypass graft patency requires cardiac catheterisation, but as this is invasive it is not suitable as a routine method or for regular examinations.

Myocardial perfusion scintigraphy with potassium-43 and rubidium-81 has been shown to be useful for evaluating the result of coronary artery bypass surgery.[9 10] Because of superior physical and biological properties thallium-201 is even more appropriate and has therefore become the most widely used radionuclide imaging agent. Even though thallium-201 exercise myocardial imaging has already been used in several studies for the postoperative analysis of myocardial perfusion, the arguments presented to date are not fully convincing. Whereas Degeorges *et al.*[11] from experience with three patients were enthusiastic about the usefulness of scintigraphy, Rosenblatt and his colleagues stated [12] that, "the role of ^{201}Tl myocardial perfusion scanning in evaluating postoperative graft status remains uncertain". In the original work of Ritchie *et al.*[13] only 11 out of the 20 patients who were examined had a complete preoperative scintigraphic evaluation including both exercise and resting images which are a prerequisite for the detection of postoperative changes in distribution of perfusion. And among the 27 patients studied by Greenberg and co-workers[14] only nine patients were examined scintigraphically before surgery. Finally, Verani *et al.*[15] could not correlate the results obtained in their 23 patients with bypass graft patency as shown by coronary arteriography.

In the present study, thallium-201 exercise myocardial scintigrams before and after operation in a group of 54 patients were analysed semiquantitatively and compared with the postoperative clinical findings and the exercise electrocardiogram. In a subgroup of 35 patients postoperative scintigraphic changes were compared with the changes in the vascular status.

Methods

Thallium-201 exercise myocardial scintigrams are carried out routinely in most of the patients suspected of having coronary artery disease in this institution. For this study 54 consecutive male patients who were to undergo coronary artery bypass surgery were selected for participation. Their ages ranged between 34 and 67 years (mean age 52 ± 8 (SD) years). All patients complained of typical stable or chronically progressive angina pectoris. Of the 54 patients, 27 had a history of previous myocardial infarction documented by typical electrocardiographic and serum enzyme changes. The preoperative scintigraphic evaluation took place 10 ± 8 weeks before operation, while the postoperative imaging study was performed on average 24 ± 10 weeks after operation. The patients were told not to take beta-blocking agents and digitalis at least during the five days preceding exercise scintigraphy; treatment with glyceryl trinitrate was continued to avoid severe anginal attacks. Thirty-five patients were recatheterised after operation at the time when the second scintigram was performed, because of persistent or recurrent chest pain in 25 of them and a postoperative myocardial infarction in two. In the eight patients who were asymptomatic coronary arteriography was repeated because the surgeons as well as the patients themselves were interested in the success of the operation.

At preoperative coronary arteriography, seven patients (13%) had single vessel disease, 17 patients (31%) had double vessel disease, and 30 patients (56%) had triple vessel disease. At operation, nine patients received a single bypass graft, and 26 received two bypass grafts; 16 patients had three bypass grafts, and three patients had four grafts. On average 2·2 bypass grafts were implanted per subject. In all instances saphenous vein homotransplants were used.

THALLIUM-201 EXERCISE MYOCARDIAL SCINTIGRAPHY

To perform myocardial imaging after exercise, the fasting patients were stressed on a bicycle ergometer in the upright position until the appearance of angina or of electrocardiographic abnormalities (see later) in the continuously recorded three lead electrocardiogram (V2/V4/V6), or until submaximal heart rate was achieved under steady state conditions. At this point 1·5 mCi thallium-201 chloride (New England Nuclear Corp., North Billerica, Mass., USA) were injected intravenously and the patient was asked to continue exercising for another two minutes. He then lay down and five minutes after stopping the exercise, imaging was begun. Scintigrams were obtained in the 45° and 60° left anterior oblique, anterior, and left lateral positions by rotating the gamma camera head over the supine patient. Using a Picker Dyna Camera 4/12 (Picker Corp., Cleveland, Ohio, USA) with a parallel hole collimator peaked within the region of 69 to 83 KeV 250 000 count analogue images were recorded either on Polaroid prints or on CRT-*x*-ray film. Data accumulation was performed by means of a PDP-11 computer (Digital Equipment Corp., Maynard, Mass., USA) using the gamma-11 programme. The images were digitised on an Elscint-CTP-System (Elscint Ltd., Haifa, Israel), enhanced by a five-point smoothing procedure and displayed in a single frame of 96 × 96 matrix elements (zooming) in eight colours, with an additional colour to indicate overrange. This preset colour count range comprising in total either 32 or 64 counts per cell was set by adjusting the base of the colour count range such that only one single cell within the myocardial wall showed overrange activity. Thus, the relative activities within the cells overlying the different regions of the myocardial wall could be calculated by comparing the number of counts per cell as indicated by its colour to the number of counts of the cells with maximal activity, that is the cells the colour of which was second to the colour indicating overrange activity in the colour count range. Background activity was assumed to be constant. This has been shown to be feasible by the experimental work of Narahara and colleagues.[16] The images were printed in full size on paper using a nine colour printer.

In a previous study[17] we compared the range of the relative activities in the different regions of the myocardial wall in a group of normal subjects and in a group of patients with arteriographically proven coronary vascular lesions of more than 50 per cent reduction in lumen diameter. Neither in the exercise nor in the resting study did the differences in the relative activities within the different regions of the wall exceed 15 per cent in the normal group, whereas in all patients with coronary artery lesions the activity within the myocardial region supplied by this artery was less than 80 per cent of the maximal activity after the exercise test. Based on this observation a perfusion defect was defined as a transmural segment with a circumferential length at least equal to wall thickness showing less than 80 per cent of maximal thallium-201 activity (Fig. 1).

Four hours after the first scintigram, when redistribution had occurred, a second series of images was obtained in the same projections as during the recording of the exercise images. These scintigrams then represented the thallium-201 distribution under resting conditions and by comparison with the exercise images one could differentiate between exercise-induced perfusion defects representing ischaemic regions and constant perfusion defects attributable to scarred tissue.

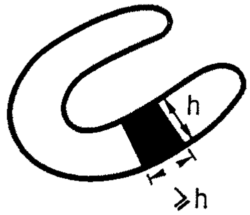

Fig. 1 *Criteria for semiquantitative assessment of thallium-201 myocardial scintigrams. A perfusion defect was defined as a transmural segment with a circumferential length at least equal to wall thickness showing less than 80 per cent of maximal thallium-201 activity.*

CATHETERISATION AND CORONARY ARTERIOGRAPHY

Pre- and postoperative cardiac catheterisation took place within three weeks after the exercise myocardial scintigraphy. After performing the left ventriculograms by biplane cineangiocardiography using 50 ml of 76 per cent Urografin® injected into the left ventricular cavity, selective coronary arteriography by the Judkins technique was carried out in multiple projections. The arteriograms were interpreted by two independent observers who were unaware of the clinical findings and the outcome of the myocardial scintigraphy. A vascular narrowing of 70 per cent or more of the lumen diameter was considered to be significant. To assess quantitatively the status of coronary vascularisation before and after operation the coronary artery lesions as well as the bypass graft patency were scored according to the proposal of Levine *et al.*[18] Thus, coronary artery narrowings of less than 70 per cent of lumen diameter as estimated from at least two different projections of the arteriogram were given the value 0. A stenotic lesion of 70 to 90 per cent was assigned the value of −0·5, and a lesion of more than 90 per cent narrowing the value −1·0. In addition, a patent graft was assigned the value +1·0 and an occluded graft the value 0. Since all patients showed at least one significant coronary artery stenosis at preoperative arteriographic evaluation, the preoperative vascularisation index (VI) was always negative, averaging −2·4 ± 1·5 (SD). According to this numerical construction, the degree of vascular obstruction is given by the negative vascularisation index of Levine (–VI).

RESTING AND EXERCISE ELECTROCARDIOGRAM

A normal 12 lead electrocardiogram at rest was recorded before operation in 35 of the 54 patients. One patient had a complete right bundle-branch block. In the remaining 18 patients the resting electrocardiogram showed the signs typical of either chronic anterior, inferior, or inferoposterior infarction, findings that corresponded to the history of previous myocardial infarction. In nine patients, however, the electrocardiogram recorded at the time of the preoperative scintigraphic evaluation disclosed no signs of chronic infarction despite well-documented characteristic changes observed during the acute event.

Exercise testing was performed by supine multistage bicycle ergometry. During the entire procedure a three lead electrocardiogram (V2/V4/V6) was continuously monitored and blood pressure taken repeatedly. The patients were stressed by stepwise increase in the workload until either chest pain or pathological electrocardiographic changes occurred or until age-predicted submaximal heart rate was achieved.

The exercise electrocardiogram was considered abnormal if a horizontal or downsloping ST segment depression occurred of more than 0·1 mV below the baseline and lasting for more than 0·08 s beyond the J point during exercise or in recovery. The sudden appearance of multiple multifocal ventricular beats or of a new complete left bundle-branch block during the stress test was also considered to indicate myocardial perfusion abnormalities.

Preoperatively, the exercise electrocardiogram was abnormal in 36 of the 54 patients (67%) and in one patient it could not be interpreted because of pre-existing complete right bundle-branch block. Thirty-three patients exhibited a typical ST segment depression and one patient with suspected anterior wall aneurysm showed a distinct elevation of the ST segment up to 0·6 mV above the baseline. In one patient the exercise test had to be terminated abruptly after the sudden onset of salvos of multifocal ventricular beats, and in another patient a complete left bundle-branch block appeared during exercise. In 35 patients anginal pain, with or without pathological electrocardiographic changes, forced termination of the exercise stress test. This type of routine exercise stress test was performed on each patient several days before myocardial exercise scintigraphy. It served to determine the workload at which clinical symptoms and/or electrocardiographic changes occurred.

STATISTICS

All results were expressed as means ± 1 SE. Paired and unpaired comparisons with Student's t test were used to evaluate the statistical significance of differences in the data within and between groups. Proportions were analysed with either the test of McNemar (paired case) or the χ^2 test (unpaired case) using Yates' correction if the sample sizes were small.[19]

Results

PRE- AND POSTOPERATIVE THALLIUM-201 SCINTIGRAMS

The *preoperative* exercise scintigrams of 51 of 54 patients showed typical, isolated zones of reduced thallium-201 uptake which filled in as redistribution occurred, thus indicating exercise-induced ischaemic regions. Moreover, in 25 of the 51 patients a second defect was identified, which persisted in the resting scintigram and thus was interpreted as representing scarred tissue. In two of the 54 patients ischaemic regions adjacent to a zone of infarction were suspected since the large perfusion defect observed after exercise was much reduced in size at rest. And finally, one of the 54 patients showed a diffuse scintigraphic pattern after exercise as well as at rest, with several spots of reduced thallium-201 uptake in different regions of the wall, suggesting diffuse myocardial disease.

Thus, exercise-induced transitory defects as evidence for stress-dependent ischaemia were unequivocally observed in 51 of the 54 patients indicating a 94 per cent sensitivity of thallium-201 exercise scintigraphy for detecting ischaemic regions in this small and highly selected group of patients. This was significantly ($p < 0{\cdot}001$) higher than the 67 per cent sensitivity of the exercise electrocardiogram which was abnormal in only 36 of the 54 patients. Constant perfusion defects caused by scarred tissue were found in 25 of the 27 patients with a previous myocardial infarction proven by electrocardiogram and serum enzyme changes, resulting in a sensitivity of 93 per cent to detect myocardial infarction; this again was higher than the 67 per cent sensitivity of the electrocardiogram at rest ($p < 0{\cdot}05$) (abnormal Q waves or loss of R wave potential in 18 of the 27 patients).

With respect to the dominant coronary lesion the scintigraphic findings corresponded closely to the results of coronary arteriography. In the seven cases with single vessel disease the vascular lesion was precisely predicted on the basis of the scintigraphic defect, whereas in the 47 cases with double or triple vessel disease multiple stenotic lesions were suspected in only 20 of them.

The *postoperative* scintigrams were examined in two steps. First they were analysed for perfusion defects (their location and size) as they occurred either in the exercise study alone or in both the exercise and resting scintigram. Secondly, the postoperative scintigrams were compared with the preoperative studies. Since the purpose of the investigation was to evaluate thallium-201 scintigraphy for its usefulness in assessing the success of coronary artery bypass surgery, the patients were classified into three groups according to the results of the postoperative scintigraphy. Group 1 comprised 31 patients in whom the preoperatively visible perfusion defects after exercise were abolished postoperatively, that is thallium-201 activity remained within normal limits (above 80% of maximal activity) in all regions of the myocardial wall except for constant perfusion defects caused by a preoperative myocardial infarction, which were seen in both studies in 19 patients. Group 2 comprised 16 patients in whom the postoperative scintigrams were identical to the preoperative ones, that is similar exercise-induced perfusion defects of identical location and size were visible in both studies. In six of these patients the preoperatively diagnosed myocardial infarction was identified postoperatively as well. Finally, group 3 comprised seven patients in whom the preoperatively observed exercise-induced perfusion defects were either more pronounced and increased in size postoperatively or additional new perfusion defects were noted. Two of the seven patients suffered a myocardial infarction which occurred postoperatively.

The relative pre- and postoperative thallium-201 activities within the preoperatively ischaemic region are shown in Fig. 2. In group 1 the relative thallium-201 activity averaged 70 ±3 per cent (means ±1 SEM) after exercise and 85 ±3 per cent at rest preoperatively ($p < 0{\cdot}001$). Postoperatively, the relative thallium-201 activity within the same region amounted to 88 ±2 per cent after exercise and 93 ±2 per cent at rest (NS). The pre- and postoperative values after exercise differed significantly at the $p < 0{\cdot}001$ level, while the pre- and postoperative values at rest were also different at the $p < 0{\cdot}02$ level, indicating severe hypoperfusion preoperatively, which resulted in incomplete redistribution within the four hours between the exercise and the resting study. In group 2 the respective values were 75 ±2 per cent after exercise and 84 ±2 per cent at rest preoperatively ($p < 0{\cdot}001$) and 74 ±3 per cent after exercise and 84 ±2 per cent at rest postoperatively ($p < 0{\cdot}001$). No significant difference existed between the pre- and postoperative values either after exercise or at rest. In group 3 the figures were 72 ±2 per cent after exercise and 76 ±4 per cent at rest preoperatively (NS) and 63 ±2 per cent after exercise and 71 ±3 per cent at rest postoperatively ($p < 0{\cdot}05$). The pre- and postoperative values after exercise differed significantly at the $p < 0{\cdot}05$ level whereas no significant difference was observed between the respective values at rest.

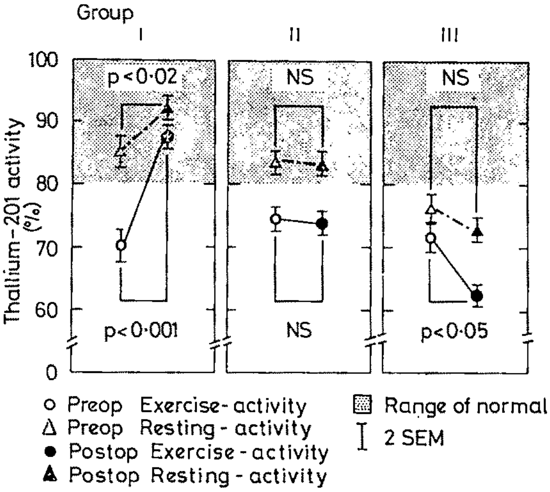

Fig. 2 *Pre- and postoperative thallium-201 activity within the ischaemic region after exercise and at rest relative to maximal myocardial thallium activity. The shaded region indicates the range of normal. Expressed are means ± 1 SEM. In group 1, comprising 31 patients, thallium activity within the dominant ischaemic region was depressed after exercise preoperatively and was within normal limits postoperatively. The significant increase in thallium activity at rest postoperatively indicates increased resting perfusion. In group 2, comprising 16 patients, thallium activity after exercise was diminished preoperatively and remained diminished postoperatively, whereas in group 3, comprising seven patients, both the thallium activity after exercise and at rest were reduced preoperatively and were found to be even more reduced postoperatively.*

In Fig. 3 the digitised scintigram in the LAO 45° position after exercise and at rest—before and after operation—of a patient in group 1 is shown. This patient who had triple vessel disease received four bypass grafts which were all patent at restudy. Apart from some slight thoracic discomfort not related to physical activity and presumably a result of sternotomy, the patient was symptom free after operation, whereas before it he had complained of severe angina. The large preoperative perfusion defect seen in the anteroseptal wall after exercise, which was related to the predominant lesion in the proximal left anterior descending coronary artery, had completely disappeared after operation.

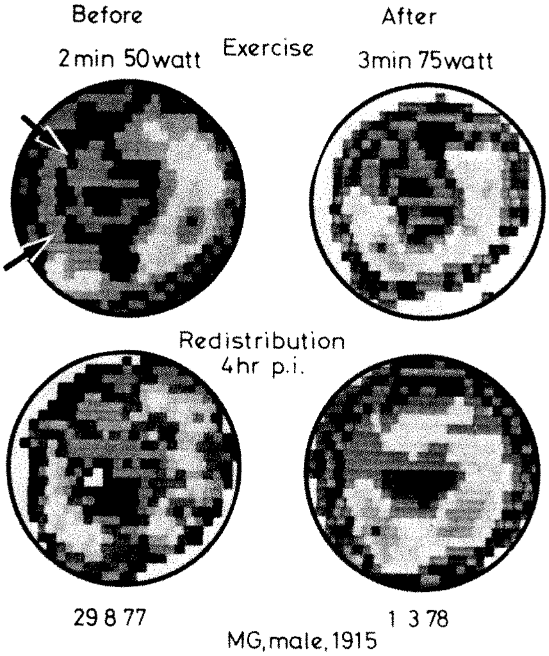

Fig. 3 *Digitised scintigram in the LAO 45° position after exercise and at rest—before and after operation—of a 63-year-old patient in group 1 with three vessel disease. A large perfusion defect in the anteroseptal wall (indicated by the arrows) was found preoperatively after exercise which filled in as redistribution occurred. This defect was related to a severe proximal lesion of the left anterior descending coronary artery. At operation the patient received four bypass grafts which were all patent at restudy. Correspondingly, the postoperative thallium scintigram disclosed normal perfusion after exercise as well as at rest in all segments of the myocardial wall.*

THALLIUM-201 SCINTIGRAM AND CLINICAL AND ELECTROCARDIOGRAPHIC FINDINGS AFTER OPERATION

As summarised in Fig. 4, the clinical symptoms, that is chest pain at rest or during physical stress, and the exercise electrocardiogram correlated poorly with the scintigraphic findings. Of the 54 patients, 22 were symptom free after operation. However, two of them showed a pathological electrocardiographic response during exercise even though no perfusion defect was found in the scintigram and the postoperative arteriographic evaluation showed complete revascularisation. In eight of the 20 patients who were symptom free and had normal exercise electrocardiograms postoperative and myocardial perfusion was unchanged as compared with the preoperative evaluation. The postoperative arteriography performed in six of these patients indicated a severe progression of the atherosclerotic disease in the native coronaries and occlusion of seven of 15 bypass grafts.

No perfusion defects could be detected in the postoperative scintigrams of 11 patients with postoperative chest pain but who had a normal exercise electrocardiogram. Nine of the 11 patients were also restudied arteriographically. In all but one patient a significant improvement in the vascularisation status was noted and only one of the 18 bypass grafts was occluded. In one patient with multiple severe vascular lesions, however, both implanted bypass grafts were occluded and a progression in severity of the lesions as well as new narrowings were found at restudy. The scintigram which, in retrospect, was found to be falsely negative should be reinterpreted as resulting from a balance of diminished perfusion in all

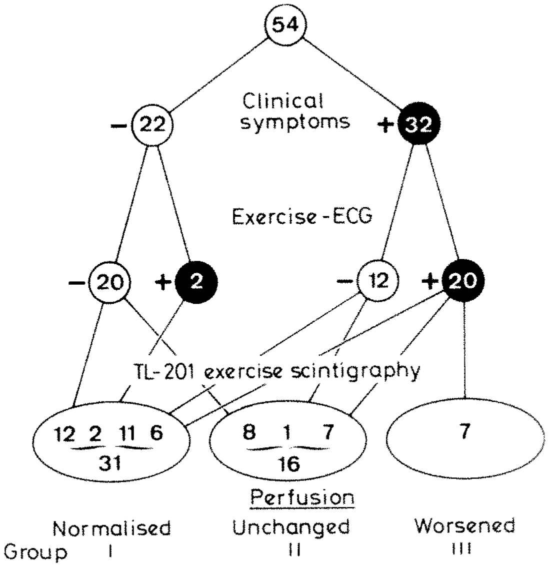

Fig. 4 *Comparison of postoperative clinical symptoms and exercise electrocardiogram in relation to thallium-201 exercise scintigraphy. Postoperatively, 22/54 patients were symptom free whereas 32/54 patients still complained of chest pain. In two of the 22 asymptomatic patients the exercise electrocardiogram was abnormal. Both patients, however, showed normal perfusion within the preoperatively ischaemic region in the thallium scintigram. In eight of 20 asymptomatic patients with normal exercise electrocardiogram the scintigram showed identical perfusion defects before and after operation. In contrast, improvement in perfusion was documented in 11/12 symptomatic patients with normal exercise electrocardiogram and in six of 20 patients who complained of chest pain after operation in whom the exercise electrocardiogram was abnormal.*

vascular beds leading to an overall reduction of thallium uptake even during exercise.

Only two of the six patients who had chest pain and a pathological exercise electrocardiogram, but who showed a normal thallium-201 scintigram postoperatively, could be restudied by coronary arteriography. In the first patient all three, and in the second patient two out of three bypass grafts were patent and showed good anterograde flow.

Among the six out of the seven patients with pronounced or new postoperative perfusion defects who were recatheterised all grafts were occluded or severely stenotic except for that in one patient in whom the two implanted bypass grafts were patent but who had sustained a large anteroseptal infarction postoperatively caused by occlusion of the left anterior descending coronary artery just distal to the site of graft implantation.

To summarise these findings, thallium-201 scintigraphy disclosed unchanged postoperative myocardial perfusion, corroborated by arteriography, in 40 per cent (8/20) of those patients who had no clinical symptoms and normal postoperative exercise electrocardiograms. Without scintigraphy these patients would have been falsely classified as being operation successes. In contrast, a failure of the surgical intervention could be excluded by the postoperative scintigram which had returned to normal in 17 of the 31 patients (53%) in whom deterioration of the myocardial perfusion status was suspected from the complaints of chest pain with or without a pathological exercise electrocardiogram.

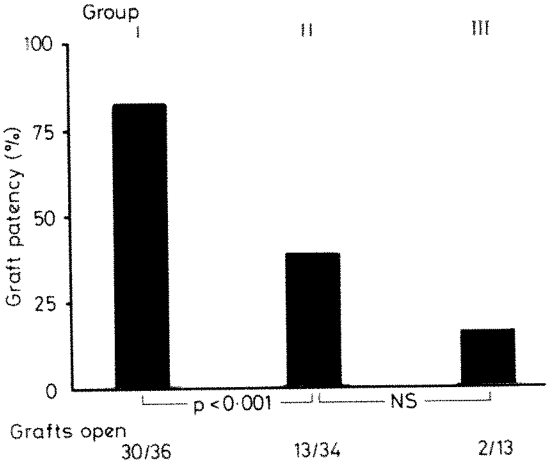

Fig. 5 *The aortocoronary bypass graft patency rate assessed in 35 out of the 54 patients by selective coronary arteriography paralleled the scintigraphic findings. It amounted to 81 per cent (30/36 grafts patent) in 16 arteriographically restudied patients out of the 31 patients who belonged to group 1 (normalised perfusion postoperatively according to the thallium scintigram). In group 2 (unchanged postoperative perfusion scintigraphically) bypass patency rate was significantly less, amounting to 38 per cent (13/34 grafts patent) in 13 of the 16 patients assigned to this group who were recatheterised. And in group 3 (worsened postoperative perfusion according to the thallium scintigram) it amounted to only 15 per cent (two of 13 grafts patent) in six out of seven patients who were restudied arteriographically in this group.*

THALLIUM-201 SCINTIGRAM AND ARTERIOGRAPHIC FINDINGS

The bypass graft patency rate paralleled the scintigraphic findings in the 35 patients who underwent an arteriographic restudy. It amounted to 81 per cent (29/36 grafts) in group 1 (16 patients restudied) which differed significantly ($p < 0·001$) from group 2 (13 patients restudied) where it amounted to 38 per cent (13/34), whereas it was only 15 per cent (2/13) in group 3 (six patients restudied) (Fig. 5).

The changes in myocardial perfusion after operation, however, depend not only upon bypass graft patency but also on the course of the atherosclerotic disease in the native vessels. Thus, it seemed appropriate to consider both the vascular lesions and the bypass graft patency, and to establish the degree of obstruction as defined by the negative value of the vascularisation index proposed by Levine *et al.*[18] The overall degree of vascular obstruction declined in group 1 from 2·1 ± 0·3 preoperatively to 1·1 ± 0·3 postoperatively ($p < 0·001$), while it remained unchanged in group 2, averaging 3·0 ± 0·4 and 3·1 ± 0·5 (NS), respectively. In group 3 it even tended to increase from 2·2 ± 0·6 preoperatively to 3·3 ± 0·6 (NS) postoperatively (Fig. 6).

Further confirmation that the results of the postoperative thallium-201 scintigraphy are intimately linked to the overall vascular status was obtained when the 35 patients with postoperative arteriography were analysed separately according to the change in their vascular obstruction index (Table). In four patients complete revascularisation (postoperative vascular obstruction index zero) was achieved by the surgical intervention. Correspondingly, thallium-201 activity after exercise within the previously ischaemic region had increased to normal. Classified according to their postoperative thallium-201 scintigram all four patients belonged to group 1. Seventeen patients showed a decrease in the obstruction index, that is an improvement in their vascularisation status after operation even though some impairment remained. The postoperative thallium-201 activity after exercise within the preoperatively ischaemic region was found to be within normal limits (83 ± 3% as compared with 72 ± 3% preoperatively, $p < 0.025$). Of the 17 patients, 11 were classified according to their postoperative thallium-201 scintigram in group 1, whereas five patients belonged to group 2, and one even to group 3; this latter patient had received two bypass grafts at operation which were found to be patent at restudy, and after operation, however, he had a large anteroseptal infarction caused by occlusion of the left anterior descending coronary artery just distal to the site of graft implantation, which led to a new perfusion defect in the postoperative scintigram.

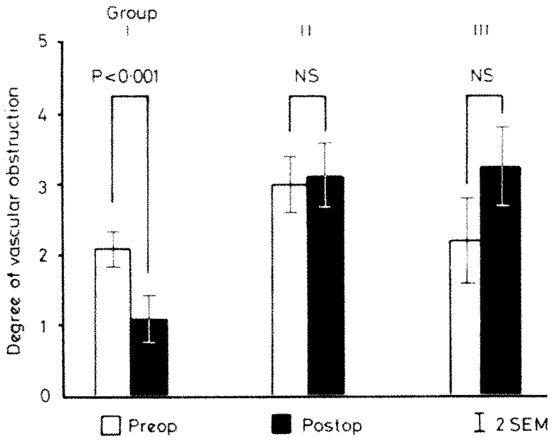

Fig. 6 *In order to establish the overall status of vascularisation before and after operation a numerical construct including all vascular lesions as well as bypass graft patency was performed similar to the one proposed by Levine* et al.[18] *in the 35 patients who underwent a postoperative arteriographic evaluation (for further explanation see text). Whereas in group 1 (normalised perfusion postoperatively according to the thallium scintigram), the degree of vascular obstruction was significantly reduced postoperatively, it remained unchanged in group 2 (unchanged postoperative perfusion scintigraphically), and even tended to be increased in group 3 (worsened postoperative perfusion).*

In eight patients the vascularisation state remained unchanged after operation, as was the thallium-201 uptake after exercise within the predominant ischaemic region. Six of these eight patients had been assigned to group 2, according to the postoperative thallium-201 scintigram, and two patients to group 3.

In six patients, finally, the vascular situation was found to have deteriorated postoperatively because of bypass occlusion, the appearance of new vascular lesions, or progression of pre-existing narrowings of ungrafted vessels. Thallium-201 uptake within the predominant ischaemic region tended to be less after operation than before. Two of the six patients had been assigned to group 2 according to their postoperative thallium-201 scintigram, three patients to group 3, and one patient to group 1; this patient had multiple vascular lesions and both bypass grafts were found to be occluded at restudy, resulting in an inhomogeneous postoperative thallium-201 scintigram without a distinct region of diminished thallium-201 uptake to meet the criterion of a true perfusion defect.

In summary, then, a correct prediction of the state of vascularisation by thallium-201 scintigraphy was achieved in 80 per cent of the patients of this subgroup (28/35: four patients with no obstruction and 11 patients with decreased obstruction had been

Table *Pre- and postoperative thallium-201 exercise scintigrams in 35 patients according to postoperative change in vascular status assessed by vascular obstruction index*

Postoperative vascular status	*No. of patients*	*Vascular obstruction index*		^{201}*Tl scintigram (% Tl-activity at exercise within ischaemic region)*		*No. of patients assigned to Tl-scintigram group*		
		Before	*After*	*Before*	*After*	*1*	*2*	*3*
No obstruction (complete revascularisation)	4	+2·0	0	58	87	4	—	—
Obstruction decreased (improved vascularisation)	17	+2·8 ±0·2*	+1·4 ±0·2	72 ±3	83 ±3	11	5	1
		p < 0·001		p < 0·025				
Obstruction unchanged	8	+3·4 ±0·7	+3·4 ±0·7	76 ±2	74 ±2	—	6	2
		NS		NS				
Obstruction increased (worsened vascularisation)	6	+1·8 ±0·3	+3·4 ±0·4	70 ±3	61 ±4	1	2	3
		p < 0·005		NS				

*Mean ± 1 SEM.

correctly assigned to group 1; from the eight patients with unchanged obstruction, six had been assigned to group 2, and two to group 3; and from the six patients with increased obstruction, two had been assigned to group 2 and three to group 3). On the other hand, the scintigraphic results did not compare with the arteriographic findings in 20 per cent (7/35: from the 17 patients with decreased obstruction, five had been assigned to group 2 and one even to group 3, and one patient with increased obstruction had been falsely assigned to group 1).

Discussion

The widespread use of coronary artery bypass surgery in the care of patients with coronary heart disease means that methods for evaluating its effect on regional myocardial perfusion are most desirable. Coronary arteriography is definitely the most direct approach to visualise bypass graft patency. Its invasive character combined with a certain risk for the patient, however, prohibits serial studies.

The clinical findings alone, even if combined with exercise testing and the recordings of the exercise electrocardiogram, may, at best, provide a rough guide in assessing the postoperative situation but clearly do not allow precise evaluation of the surgical treatment.

Thus, radionuclide techniques because they are noninvasive and readily available have been suggested as useful methods of determining the effect of coronary revascularisation procedures. Gated radionuclide cineangiography allows assessment of left ventricular ejection fraction and regional contraction not only at rest but also during exercise.[20 21] The accuracy of the method during exercise, however, needs further validation by comparison with contrast angiography. In contrast to this technique which aims to detect functional abnormalities myocardial scintigraphy allows disturbances in regional myocardial perfusion to be seen. Among the different isotopes available for this purpose thallium-201 has been shown to be best suited for myocardial imaging since it has the most favourable physical and biological properties.[22 23]

Indeed, the results obtained from postoperative thallium-201 exercise myocardial scintigraphy in other studies[13 14 24] suggest the usefulness of the method if they are compared with the findings of postoperative coronary arteriography. Some criticism is, however, appropriate since thallium-201 scintigrams are most often interpreted by visual analysis of the analogue images only, and are thus dependent upon the experience of the examiner. Furthermore, the interpretation of the postoperative scintigram is more difficult than that of the preoperative one because the improvement of flow to previously ischaemic regions may result in complex changes in the thallium distribution pattern especially if more than one bypass graft has been implanted. In addition, the surgical procedure by itself may lead to alterations in the scintigraphic appearance of the heart. To draw definite conclusions about the status of vascularisation it seems mandatory to compare carefully the postoperative and preoperative scintigrams.

The results of the present study show that by applying a semiquantitative criterion to the scintigrams and by careful comparison of the pre- and postoperative images, thallium-201 scintigraphy is a reliable and useful method of assessing the success of coronary artery bypass surgery. Thus, a correct prediction of either complete or at least improved vascularisation was achieved by scintigraphy in 15 out of 16 (94%) patients classified in group 1 (Table). The postoperatively unchanged or even worsened thallium scintigrams found in 19 of the 35 patients corresponded in 13 of them (68%) with the unchanged or worsened vascular situation detected arteriographically after operation. In the remaining six patients with unchanged or worsened thallium scintigrams after operation the vascularisation was improved. In fact, it could not be determined, except by thallium scintigraphy, whether perfusion really had been altered postoperatively in these patients, since no complete vascularisation resulted from the surgical intervention and six of the 16 implanted bypass grafts were found to be occluded.

As compared with the postoperative exercise electrocardiogram the postoperative thallium scintigrams were of greater diagnostic accuracy. Whereas in only one out of the 16 (6%) patients who had a *normal* postoperative thallium scintigram (group 1 in the Table) did the preoperative scintigram have to be reassessed after arteriography as having been falsely normal, the postoperative exercise electrocardiograms were pathological in four patients (25%). On the other hand, the postoperative exercise electrocardiograms were pathological in only eight of the 13 patients (62%) with a postoperative unchanged or even worsened thallium scintigram and an arteriographically proven unchanged or deteriorating vascular situation.

In respect of clinical symptoms, all except one of the 16 patients with *normal* postoperative thallium scintigrams indicating better or complete vascularisation had improved. But only eight of them (50%), however, were totally symptomless, the remainder still having some chest pain. In contrast, of the 13 patients with postoperatively unchanged or worsened myocardial perfusion and unchanged or deteriorating vascularisation, two were entirely symptom free and five patients had clearly improved.

In conclusion, the clear relation between the changes in perfusion after operation as assessed scintigraphically and the bypass graft patency rate and degree of vascularisation, respectively, show that thallium-201 exercise scintigraphy is a useful and reliable method for documenting the success of this intervention. Scintigraphy is superior to the clinical evaluation of the patients and to the standard routine examination such as the exercise electrocardiogram. Though any prediction of bypass graft closure has to be made with caution since a postoperatively identical or even deteriorated perfusion may result from progression of the disease in the native vessels as well, the method helps to determine with good precision whether postoperative arteriographic re-evaluation is necessary. Moreover, the method is suitable for long-term follow-up of patients who have undergone coronary artery bypass surgery. Finally, combination of scintigraphy with other radionuclide techniques capable of assessing left ventricular function and regional wall motion may even further increase the sensitivity and specificity of this kind of approach and broaden knowledge of overall cardiac function in these patients.

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Br Heart J 1980; **43:** 436–9

Surgery of post-myocardial infarction scars
Early and late results in 70 patients

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SUMMARY Immediate and late postoperative results in 70 patients undergoing resection of a true left ventricular aneurysm (50 patients) and of an asynergic area (20 patients) are presented. The operative mortality was 14 per cent. Predicted survival by actuarial methods was 80 per cent at one year after operation and 65 per cent at six years. Functional improvement was obvious with most of the survivors falling in NYHA class I or II. Factors influencing operative mortality were the clinical indication for operation and the anatomical lesion. Late postoperative results were better for true aneurysms than for asynergic areas.

An asynergic area was usually associated with multiple coronary vessel lesions and a diffusely ischaemic myocardium. An aneurysm was often associated with a single coronary vessel disease and with good function of the non-infarcted myocardium.

The first successful excision of a left ventricular aneurysm was performed over 20 years ago.[1] Since then many other authors have reported their experience. Most of these reports included surgical resection of asynergic areas of the left ventricular wall as well as of true ventricular aneurysms. Little attention has been directed toward the influence of the anatomical type of left ventricular abnormality on surgical results. We present early results and long-term follow-up in a group of 70 consecutive patients, emphasising the role of the anatomical lesion of the left ventricular wall.

Patients and methods

Between December 1968 and December 1976, 70 patients with left ventricular scar secondary to myocardial infarction underwent surgery. Fifty-nine patients were men and 11 women with an age range of 30 to 70 years (mean 55 years). All patients had suffered one or two documented myocardial infarctions. In 54 patients, infarction was more than three months old. In 14 patients, infarction had occurred less than three months before operation, and in two patients it had occurred less than three weeks before.

Indications for surgery are summarised in Table 1. Congestive heart failure (40%) and ventricular arrhythmia (20%) were the two main reasons. In 21 patients (30%) operation was performed for a combination of factors, most often ventricular arrhythmia complicated by congestive heart failure.

Table 1 *Myocardial resection: surgical indication in 70 patients*

Indication	*No. of patients*	*Percentage of patients*
Congestive heart failure	28	40
Ventricular arrhythmia	14	20
Angina pectoris	7	10
Mixed	21	30
Total	70	100

In earlier patients surgery was undertaken on a clinical basis alone. Subsequently, selective coronary arteriography was performed in 61 patients (87%). Significant lesions were found in three vessels in 12 (20%), in two vessels in 22 (36%), and in one major vessel in 27 patients (44%).

In 29 patients there was a contraindication to aortocoronary bypass: six had diffuse multivessel disease or one vessel disease not suitable for revascularisation, and 23 had one vessel disease corresponding to the aneurysmal or asynergic area. Operation was performed under cardiopulmonary bypass with moderate hypothermia. In 39 patients, operation was limited to left ventricular wall resection. For these cases, the aorta was not cross-

Received for publication 18 September 1979

clamped and the heart was kept beating throughout the procedure. The 31 remaining patients had a combination of left ventricular wall resection and saphenous vein aortocoronary bypass graft (22 single grafts, seven double, and two triple). For these cases, the aorta was cross-clamped for 15 minutes during peripheral anastomoses. One patient had an additional mitral valve replacement, and three underwent closure of a ventricular septal defect.

Pathology of left ventricular scar

In 50 cases, the left ventricular scar was considered as a true aneurysm, because of: (1) a discrete border between the left ventricular chamber and the bulging area on the left ventricular cineangiogram; (2) a clear-cut limit between healthy muscle and fibrous tissue at the time of operation; and (3) a transmural lesion, the entire thickness of muscle being replaced by thin, homogeneous fibrous tissue. Among these 50 aneurysms, 41 were anterior and nine were inferior.

In the remaining 20 patients, the left ventricular scar was considered as a segmental dyskinetic area because of the absence of the above criteria. There was less bulging, more diffuse fibrous scarring of the left ventricular wall, and no discrete limit between scar and healthy muscle. In those cases, coronary artery lesions were more frequently diffuse than in true ventricular aneurysm (Table 2). Among patients with only one vessel involved, 86 per cent had a true ventricular aneurysm ($p < 0.05$).

Table 2 *Main differences between 44 aneurysms and 17 asynergic areas—61 coronary angiograms*

Anatomical lesion	*Coronary disease*		*Aortocoronary bypass*	
	One major vessel	*Two or three major vessels*	*Grafted*	*Not grafted*
Aneurysm	23	21	18	26
Asynergic area	4	13	14	3
	$p < 0.05$		$p < 0.01$	

Results

EARLY POSTOPERATIVE COURSE

Ten of the 70 patients died in the perioperative period (14%). One patient died during the surgical procedure from acute myocardial failure. Six postoperative deaths were caused by a low cardiac output syndrome without evidence of recent myocardial infarction. Two deaths were the result of infection. Anticoagulant therapy caused an additional death.

Operative mortality in this group was not related to age (as an independent factor), time elapsing between myocardial infarction and operation, presence or absence of aortocoronary bypass grafts, emergency conditions, duration of cardiopulmonary bypass, or to duration of aortic cross-clamping.

Statistically significant factors influencing mortality rate were: (1) nature of indication for operation and (2) type of anatomical lesion. Among 49 patients operated on for one single complaint (congestive heart failure or ventricular arrhythmia or angina pectoris) four died, while there were six deaths in the group of 21 patients having a double or triple reason for surgery ($p < 0.001$).

Aneurysm resection accounted for five deaths among 50 patients (10%) while resection of asynergic areas led to five deaths in a group of 20 patients (25%) ($p < 0.01$, Table 3).

Table 3 *Factors influencing operative mortality*

Patients	*Indication*		*Anatomical lesion*	
	Single	*Double or triple*	*Aneurysm*	*Asynergic area*
No. of patients	49	21	50	20
No. of survivors	45	15	45	15
No. of deaths	4 (8%)	6 (30%)	5 (10%)	5 (25%)
	$p < 0.001$		$p < 0.01$	

Combined analysis allowed us to separate high- and low-risk groups. High-risk patients had at least two of the three following factors: (1) age over 50; (2) surgery decided upon for more than one complaint; and (3) a left ventricular lesion considered to be asynergic. In this group, operative mortality was 30 per cent (9/31). Low-risk patients had at least two of the following descriptors: (1) age under 50; (2) operation decided upon for one single reason; and (3) a true aneurysm. In this group, operative mortality was 2·5 per cent (1/39), a significantly lower rate ($p < 0.01$).

LATE POSTOPERATIVE COURSE

Survival was studied by the actuarial method (Fig. 1). Including the initial fall caused by operative mortality, predicted survival was 80 per cent one year after operation and 65 per cent six years after operation.

Long-term results were estimated in 46 of the 70 patients for whom postoperative follow-up was begun two years before the beginning of the study (mean 47 months, maximum eight years). Five of these patients died from cardiac causes, three from extracardiac causes between two and 18 months after operation (mean nine months), and five had dropped out. Among the 33 long-term survivors, six had been operated on for intractable ventricular arrhythmia. Only one of these patients experienced

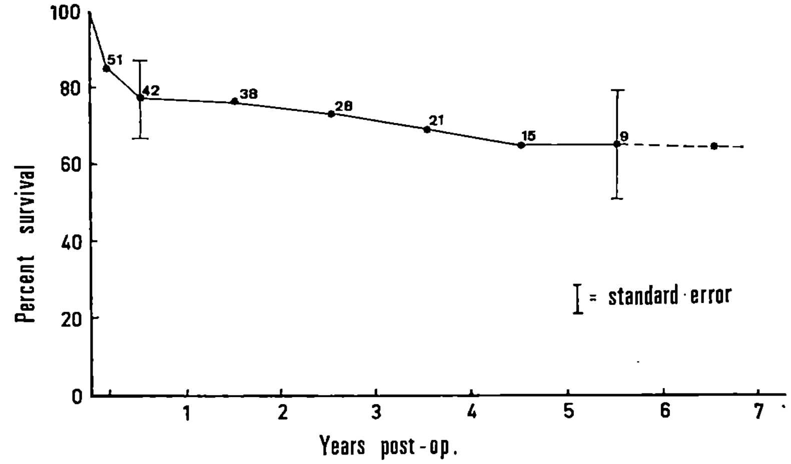

Fig. 1 *Actuarial survival curve after left ventricular resection for the entire group of 70 patients.*

recurrence of ventricular tachycardia. Left ventriculography in this patient showed the recurrence of a posterior aneurysm which was successfully resected 27 months after the first operation.

Fig. 2 shows the functional results in 27 patients operated on for cardiac failure or angina pectoris or both. Only two patients of this group were still in class III and no patient was considered to belong to class IV of the NYHA.

The only significant factor influencing long-term results in this series was the anatomical type of left ventricular wall lesion (Table 4). In all 26 patients operated on for a true ventricular aneurysm the result was satisfactory. In 12 patients operated on for an asynergic area, favourable results were observed in five patients only ($p < 0{\cdot}001$).

Table 4 *Late postoperative course and anatomical lesion*

Patients	*Aneurysm*	*Asynergic area*	
31 class I–II	26	5	$p < 0{\cdot}001$
5 cardiac deaths and two class III	0	7	

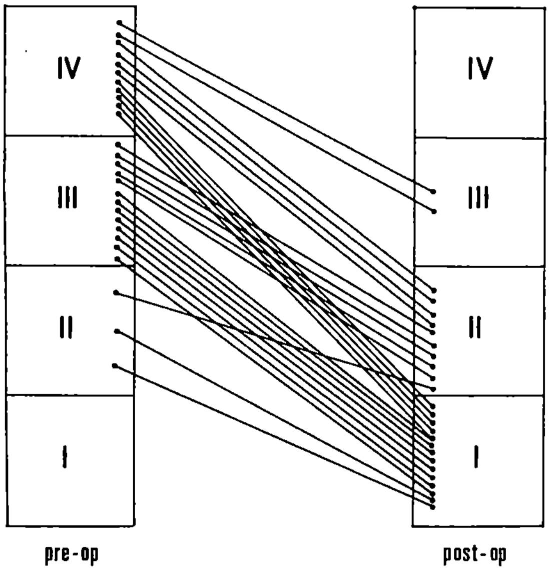

Fig. 2 *Late postoperative results (NYHA criteria). Average follow-up interval was 41 months.*

Discussion

The results of this series are primarily clinical. Postoperative catheterisation was performed only in poor surgical results. Other authors have outlined a reasonably good correlation between clinical, haemodynamic, and angiographic results.[2–4] Futhermore, contractile function is difficult to investigate in postmyocardial infarction scars. Methods such as ejection fraction and percentage of circumferential shortening of contractile segments[5 6] remain to be evaluated in preoperative prognosis.

An operative mortality of 14 per cent is comparable to other series which range from zero to 18 per cent.[4 7–10] In a previous report of our group[11] mortality was 5 per cent.

The incidence of patients operated on for ventricular arrhythmias is higher in this series (20%) than in the published reports. Efficiency of operation in these cases is obvious, since the only recurrence of ventricular tachycardia was related to the recurrence of a posterior aneurysm.

A clear-cut distinction between true ventricular aneurysms and asynergic areas is sometimes difficult to establish, especially in the first weeks after myocardial infarction. But if angiographic and operative findings are analysed in an integrated way looking for the border area between scar and healthy muscle, then even a few days after the acute event this border can usually be precisely drawn in true ventricular aneurysms.

Several reasons explain the striking difference in the results of resection of true aneurysms versus asynergic areas. (1) In true aneurysm the entire scar can be excised, whatever its size, leaving only the few millimetres of fibrous tissue necessary for a firm suture. In asynergic areas, excision takes off the most diseased part of a diffusely scarred left ventricular wall. (2) From a haemodynamic point of view, resection of a true aneurysm is more efficient than excision of a dyskinetic zone, for the impairment of left ventricular function is probably more important in the former condition. (3) In true aneurysm, coronary artery lesions are very often limited to the vessel responsible for the myocardial infarction. In asynergic areas, coronary artery disease is usually more diffuse. Though aorto-coronary bypass grafts are beneficial in patients with angina pectoris, their efficiency in improving myocardial contraction is questionable.[12 13]

We thank Dr Mark Perlroth, Department of Medicine, Stanford University School of Medicine, for reviewing and criticising the manuscript.

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Br Heart J 1980; **43:** 440–6

Haemodynamic effects of nifedipine in heart failure

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SUMMARY Nifedipine, a calcium antagonist with strong vasodilatating effects, has been successfully used in the treatment of angina pectoris. To investigate if it can be used as a vasodilator in patients with congestive heart failure, nifedipine 20 mg was administered sublingually to 11 patients with chronic heart failure. The clinical diagnosis was congestive cardiomyopathy in 10 and severe mitral regurgitation in one patient. All patients were studied haemodynamically and in 10 of them an angiographic study was also performed.

Nifedipine lowered mean systemic arterial pressure (from 95·0±5·3 to 75·2±3·6 mmHg), mean pulmonary arterial pressure (from 37·9±3·1 to 28·0±2·4 mmHg), mean pulmonary capillary wedge pressure (from 25·2±2·0 to 16·7±1·7 mmHg), left ventricular end-diastolic pressure (from 22·6±1·8 to 14·2±1·7 mmHg), and systemic vascular resistance (from 1967±247 to 1108±146 dynes s cm^{-5}). Simultaneously all indices of left ventricular performance improved: cardiac index rose from 2·12±0·11 to 3·11±0·30 l/m^2 per min, ejection fraction increased from 0·26±0·02 to 0·41±0·05 per cent, and stroke volume index rose from 32·2±1·9 to 46·8±3·4 ml/m^2. Left ventricular end-diastolic volume index and end-systolic volume index both diminished (from 137·2±14·0 to 128·1±14·3 ml/m^2 and from 104·9±13·6 to 81·3±14·7 ml/m^2, respectively). No significant changes in heart rate were noted, whereas a slight general improvement in left ventricular wall motion was seen.

In patients with congestive heart failure, there were no negative inotropic effects but an improvement in left ventricular performance in all patients, caused by a decrease in afterload secondary to the strong vasodilatating effect of the drug.

Further studies should document the possibility of nifedipine being used as an alternative to other afterload reducing agents in the chronic treatment of heart failure.

Systemic vasodilator drugs have been used increasingly during recent years in the treatment of heart failure.[1–3] These agents decrease the oxygen consumption and enhance the performance of the failing heart,[4] by reducing left ventricular wall tension in systole (afterload) and/or decreasing systemic venous return.

Nifedipine is a drug with a calcium antagonist action which has proved to be particularly effective in the treatment of angina pectoris.[5–7] The main actions of this drug in man are a reduction of peripheral resistance[8 9] and an increase in coronary flow especially in post-stenotic areas.[10 11]

Considering its effects on the peripheral resistance vessels and the low incidence of side effects,[12] nifedipine may be useful as a vasodilator in the treatment of chronic heart failure.

The purpose of this study is to evaluate the acute haemodynamic effects of the administration of nifedipine in patients with chronic congestive heart failure.

Received for publication 25 May 1979

Subjects and methods

Studies were made on 11 patients (age 41 to 67 years) with persistent heart failure despite appropriate treatment with digitalis, diuretics, and salt restriction (Table 1). The clinical diagnosis was congestive cardiomyopathy in 10 patients and congestive heart failure secondary to severe mitral regurgitation in one patient. Severe exertional dyspnoea was the predominant symptom and all the patients had radiographic cardiomegaly and upper lobe blood redistribution. There was no history of ischaemic heart disease. Informed consent was obtained from all patients. Diuretics were withdrawn 24 hours before the procedure. The day before the study, nifedipine, 10 mg, was given sublingually and the blood pressure was measured at

10-minute intervals during 40 minutes of observation.

CARDIAC CATHETERISATION

At the time of the study the patients were in a fasting state without premedication. Either a Cournand (7 or 8 F) or an angiographic (7 F) end-hole catheter was placed in the pulmonary artery via an antecubital vein. Left heart catheterisation was performed either by a brachial artery cutdown using a Lehman catheter (7 or 8 F) or by the Seldinger technique using a pigtail catheter (8 F). A polythene catheter (PE 205) was inserted in the descending aorta (Seldinger technique). In eight patients a right atrial catheter was placed (Cournand 6 or 7 or NIH 6 F) via the left femoral vein.

All pressure measurements were recorded on an Electronics for Medicine VR 6 recorder, with P 23 Db Statham strain gauge transducers and zero was set at the mid-chest level. Heart rate was averaged from recordings of a standard electrocardiographic lead. Cardiac output was determined by the Fick technique using a three-minute collection of expired air.

Thirty degrees right anterior oblique left ventricular cineangiograms (64 frames/s) were obtained both before and 40 minutes after nifedipine by the injection of 45 to 60 ml of Urografin 76 (meglumine diatrizoate and sodium diatrizoate) at 12 to 18 ml/s in 10 patients. In one patient (case 11) angiography was not performed because of the risk of pulmonary oedema.

QUANTITATIVE ANGIOGRAPHIC MEASUREMENTS AND CALCULATIONS

Quantitative angiographic measurements were obtained using a light-pen computer system (Mennen Greatbatch system 939 digital PDP 11 computer) which employs the area-length method of Sandler and Dodge.[13]

Segmental wall motion was quantified according to the method of Leighton *et al.*[14] Both premature and the first postpremature beats were excluded. For the patients (cases 1 and 4) in atrial fibrillation three cardiac cycles were averaged. The following calculations were made: CI = CO/BSA (l/min per m^2); SVR = 80 × ($\overline{AP}$ − $\overline{RA}$)/CO (dynes s cm^{-5}); PVR = 80 × ($\overline{PA}$ − $\overline{PCW}$)/CO (dynes s cm^{-5}); TPR

Table 1 *Biographical data and baseline haemodynamic values*

Case no.	*Age (y)*	*Sex*	*Diagnosis*	*Period*	*CI (l/m^2 per min)*	*HR (beats/min)*	$\overline{SAP}$ *(mmHg)*	$\overline{RAP}$ *(mmHg)*	$\overline{PA}$ *(mmHg)*	$\overline{PCW}$ *(mmHg)*	*LVEDP (mmHg)*
1	59	M	COCM, AF	C	2·4	98	114	6	41	22	24
				B	2·4	98	114	6	41	22	24
2	45	M	COCM	C	1·9	74	96	3	14	5	9
				B	2·0	60	98	5	23	13	14
3	57	M	COCM	C	2·4	60	100	7	17	15	21
				B	2·6	63	114	7	21	20	32
4	64	M	COCM, AF	C	1·8	70	73	7	32	23	15
				B	2·1	70	76	5	28	25	14
5	63	M	COCM	C	3·1	84	115	7	40	27	19
				B	2·3	90	100	8	35	28	18
6	63	M	COCM	C	2·2	80	92	6	36	27	24
				B	2·5	80	96	7	44	30	26
7	67	M	COCM	C	1·6	70	140	15	60	28	20
				B	1·6	70	120	16	55	29	18
8	56	M	COCM	C	2·0	71	76	12	35	33	30
				B	2·0	70	75	12	37	33	30
9	66	F	CHF, MR	C	1·5	100	104	6	45	35	22
				B	1·4	95	105	9	45	37	23
10	41	M	COCM	C	2·4	80	74	12	40	25	23
				B	2·4	88	74	18	47	28	24
11	55	M	COCM	C	—	—	—	—	—	—	—
				B	2·0	76	74	8	41	28	26
Mean ± SEM (11 patients)				B	2·12 ±0·11	78·1 ±3·9	95·0 ±5·3	9·3 ±3·1	37·9 ±3·1	25·2 ±2·0	22·6 ±1·8
Mean ± SEM (10 patients)				C	2·13 ±0·15	78·7 ±4·0	98·4 ±6·7	8·1 ±1·1	36·0 ±4·1	24·0 ±2·7	20·8 ±1·7
				B	2·13 ±0·12	78·4 ±4·3	97·2 ±5·4	8·7 ±1·1	37·6 ±3·4	26·5 ±2·1	22·3 ±1·9
p value C vs B (10 patients)					NS	NS	NS	NS	NS	< 0·01	NS

COCM, congestive cardiomyopathy; CHF, congestive heart failure; AF, atrial fibrillation; MR, mitral regurgitation; C, initial haemodynamic values; B, haemodynamic values immediately before nifedipine administration; CI, cardiac index; HR, heart rate; SAP, mean systemic arterial pressure; $\overline{RAP}$, mean right atrial pressure; $\overline{PA}$, mean pulmonary artery pressure; $\overline{PCW}$, mean pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure.

$=80\times\overline{PA}/CO$ (dynes s cm^{-5}), where CI = cardiac index, CO = cardiac output, BSA = body surface area, $\overline{AP}$ = mean aortic pressure, SVR = systemic vascular resistance, $\overline{RA}$ = mean right atrial pressure, 80 = factor for converting resistance units to dynes s cm^{-5}, PVR = pulmonary vascular resistance, $\overline{PA}$ = mean pulmonary artery pressure, $\overline{PCW}$ = mean pulmonary capillary wedge pressure, TPR = total pulmonary resistance.

STUDY PROCEDURE

Heart rate, systemic arterial, right atrial, pulmonary arterial, pulmonary wedge, and left ventricular pressures were recorded. Cardiac output was determined. Left ventricular angiography was performed and immediately afterwards all the pressure measurements were repeated. At five-minute intervals the left ventricular end-diastolic pressure was measured until it returned to control values and then all the control measurements were repeated. In those patients in whom the left ventricular end-diastolic pressure remained high, a maximum of 30 minutes elapsed[15] before control measurements were repeated.

Nifedipine 20 mg was then administered sublingually. All pressures were recorded after 10, 20, and 30 minutes. Cardiac output was determined 20 and 30 minutes after the drug was administered. At 40 minutes a second left ventriculogram was performed. All the measurements (except cardiac output) were recorded immediately afterwards.

All values were expressed as mean ± SEM. Student's t test on paired data was used for statistical analysis. P values $<0{\cdot}05$ were considered significant.

Results

The haemodynamic data before and 30 minutes after the 20 mg sublingual dose of nifedipine are shown in Table 2. All patients responded with an increase in cardiac index (mean increase +46%), which was moderate in some, but in two cases was more than 70 per cent (cases 2 and 11). The substantial increase in cardiac index was accompanied by a distinct decrease in systemic vascular

Table 2 *Haemodynamic effects of nifedipine*

Case no.	*Period*	*CI (l/m² per min)*	*HR (beats/min)*	*$\overline{SAP}$ (mmHg)*	*$\overline{RAP}$ (mmHg)*	*$\overline{PA}$ (mmHg)*	*$\overline{PCW}$ (mmHg)*	*LVEDP (mmHg)*	*SVR (dynes s cm^{-5})*	*PVR (dynes s cm^{-5})*	*TPR (dynes s cm^{-5})*
1	B	2·4	98	114	6	41	22	24	2032	357	771
	N	3·3	87	82	6	21	15	9	1021	80	282
2	B	2·0	60	98	5	23	13	14	2199	236	544
	N	5·5	80	72	3	15	5	5	604	87	131
3	B	2·6	63	114	7	21	20	32	1505	14	295
	N	3·2	80	90	7	18	8	10	951	114	206
4	B	2·1	70	76	5	28	25	14	1682	71	663
	N	2·3	60	64	5	23	21	11	1285	43	501
5	B	2·3	90	100	8	35	28	18	1562	118	594
	N	2·7	113	96	8	32	22	13	1285	146	467
6	B	2·5	80	96	7	44	30	26	1663	261	822
	N	3·5	76	81	3	28	18	12	1045	134	375
7	B	1·6	70	120	16	55	29	18	3364	841	1779
	N	2·3	60	72	11	36	23	15	1401	298	827
8	B	2·0	70	75	12	37	33	30	1371	87	805
	N	2·3	66	65	12	37	22	24	1004	284	701
9	B	1·4	95	105	9	45	37	23	3639	303	1706
	N	1·8	90	84	4	27	17	15	2318	289	1000
10	B	2·4	88	74	18	47	28	24	1018	345	854
	N	3·7	82	63	13	39	28	20	588	129	458
11	B	2·0	76	74	10	41	28	26	1600	315	994
	N	3·5	82	59	9	32	21	23	689	151	441
Mean ± SEM	B	2·12 ± 0·11	78·1 ±3·9	95·0 ±5·3	9·3 ±1·3	37·9 ±3·1	25·2 ±2·0	22·6 ±1·8	1967 ±247	268 ±67	893 ±138
	N	3·11 ± 0·30	79·6 ±4·5	75·2 ±3·6	7·3 ±1·0	28·0 ±2·4	16·7 ±1·7	14·2 ±1·7	1108 ±146	159 ±27	490 ±79
p value		<0·01	NS	<0·0005	<0·025	<0·001	<0·00025	<0·0025	<0·0005	NS	<0·001

B, haemodynamic values immediately before nifedipine administration; N, haemodynamic values 30 minutes after nifedipine administration; CI, cardiac index; HR, heart rate; $\overline{SAP}$, mean systemic arterial pressure; $\overline{RAP}$, mean right atrial pressure; $\overline{PA}$, mean pulmonary artery pressure; $\overline{PCW}$, mean pulmonary capillary pressure; LVEDP, left ventricular end-diastolic pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; TPR, total pulmonary resistance.

resistance (−43%) and by a moderate decline in mean systemic arterial pressure (−21%). Left ventricular end-diastolic pressure fell in all patients (−37%). Mean pulmonary artery and mean pulmonary wedge pressures decreased significantly (−26 and −34%, respectively). Only six patients showed a change in mean right atrial pressure. The average decline was −21 per cent and was significant ($p < 0·025$). Pulmonary vascular resistance fell by an average of 40 per cent but this change was not significant. In the seven patients with high resistances (> 120 dynes s cm^{-5}), this fall was significant (Fig. 1) and was well correlated with the pretreatment values (Fig. 2).

There was no significant change in heart rate: four patients had a small increase, and seven patients a small decrease in heart rate.

Angiographic results are shown in Table 3. All patients showed an increase in stroke volume and ejection fraction (+45 and +57%, respectively) and a decrease in left ventricular end-systolic volume (−22%). Left ventricular end-diastolic volume decreased significantly (−6%), but in two patients (cases 7 and 10) showed a slight increase. Changes in segmental systolic shortening are shown in Fig. 3.

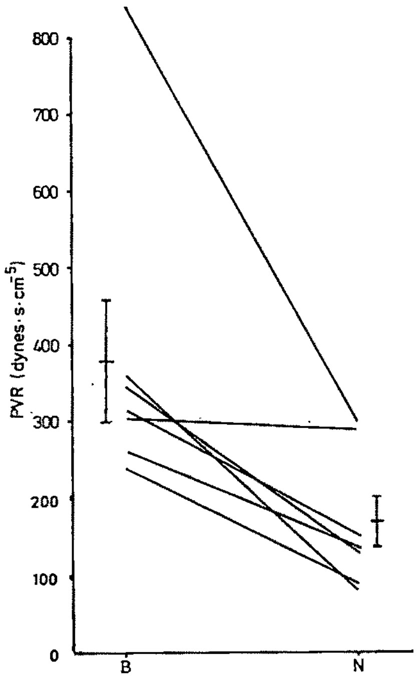

Fig. 1 *Change in pulmonary vascular resistance after nifedipine administration in the seven patients with high (> 120 dynes s* cm^{-5}*) resistance (mean ± SEM). Cases 1, 2, 6, 7, 9, 10, 11. B, basal; N, nifedipine.*

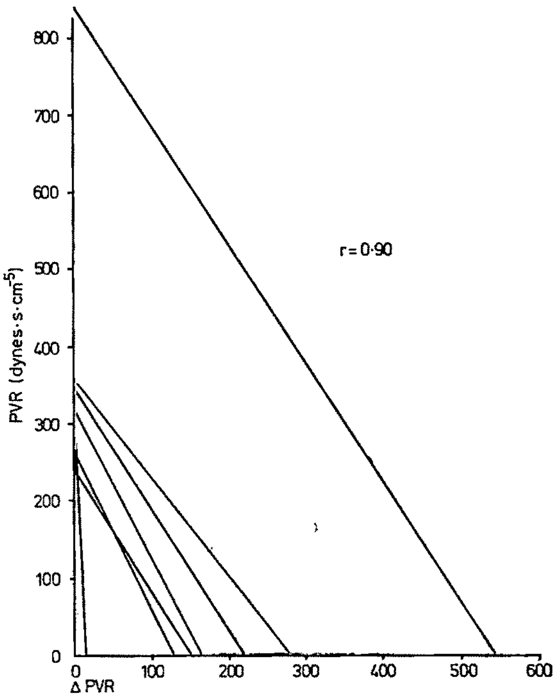

Fig. 2 *Fall in pulmonary vascular resistance (ΔPVR) compared with initial values (PVR) in seven patients of Fig. 1.*

Discussion

Congestive heart failure is characterised by a decreased cardiac output and an augmented left ventricular end-diastolic pressure. An increase in systemic vascular resistance helps to maintain systemic arterial pressure, but this leads to augmented impedance to left ventricular ejection. Systemic vasodilators may interrupt this vicious cycle by increasing left ventricular emptying and diminishing myocardial oxygen consumption,[4] and they are assuming a new role in the treatment of heart failure.[2 3] Nifedipine is a calcium antagonist drug which reduces systemic vascular resistance.[9 16] This effect (with the consequent reduction in left ventricular afterload) and the increase in coronary flow[10 11] are the main mechanisms of action of this drug in ischaemic heart disease. The rapidity and efficacy of nifedipine mediated reduction of peripheral resistance,[9] moreover, suggested that it might represent a first choice drug in hypertensive emergencies.[16] The negative inotropic action of nifedipine, initially described in the isolated heart muscle preparation,[17] was not shown in the haemodynamic studies which followed in man. The pronounced vasodilatating effect, not accompanied by any change in contractility, may be explained by the in vitro observation that the excitation-contraction coupling of vascular smooth muscle is three to 10 times more sensitive than myocardial fibres to the action of calcium antagonist drugs.[18] The vasodilatating effect, therefore, can be achieved even at a dosage inadequate to act on myocardial contractility. In haemodynamic studies in man a slight increase in peak dP/dt has been observed in some subjects.[9 16 19] This may be a result of the baroceptor mediated response to a fall in arterial pressure. In this study nifedipine was used to reduce impedance to ventricular emptying in a group of patients suffering from chronic congestive heart failure.

In the group studied, nifedipine determined important haemodynamic changes (Table 2). There was a significant fall in mean pulmonary artery, mean aortic, and left ventricular end-diastolic pressure, a decrease in systemic vascular and total pulmonary resistance, and a significant increase in cardiac index. Angiographic derived data (Table 3) also showed an improvement in left ventricular performance, as evidenced by an increase in ejection fraction and stroke volume and a decrease in both left ventricular end-diastolic and end-systolic volumes. Segmental shortening analysis (Fig. 3) indicated a diffuse hypokinesis in all patients and showed a general but not statistically significant improvement.

Table 3 *Changes in angiographic derived values after nifedipine*

Case no.	*Period*	*LVEDVI (ml/m²)*	*LVESVI (ml/m²)*	*SVI (ml/m²)*	*EF (%)*
1	C	111·2	77·4	33·9	0·30
	N	92·4	56·5	35·9	0·39
2	C	113·5	85·1	28·4	0·25
	N	106·6	45·7	60·9	0·57
3	C	109·8	70·3	39·4	0·36
	N	93·2	27·6	65·6	0·70
4	C	167·8	146·4	21·4	0·13
	N	160·3	123·1	37·2	0·23
5	C	91·9	59·7	32·2	0·35
	N	82·6	49·8	32·8	0·40
6	C	178·8	146·1	32·8	0·18
	N	163·6	120·5	43·1	0·26
7	C	67·3	41·5	25·8	0 38
	N	70·4	27·4	43·0	0·61
8	C	171·4	132·1	39·3	0·23
	N	158·4	112·7	46·2	0·29
9	C	153·1	123·3	29·7	0·19
	N	143·6	86·8	56·8	0·40
10	C	207·0	167·5	39·5	0·19
	N	210·1	162·9	47·2	0·22
Mean ± SEM	C	137·2 ± 14·0	104·9 ± 13·6	32·2 ±1·9	0·26 ±0·02
	N	128·1 ± 14·3	81·3 ± 14·7	46·8 ±3·4	0·41 ±0·05
p value		<0·005	<0·00025	<0·0025	<0·0025

LVEDVI, left ventricular end-diastolic volume index; LVESVI, left ventricular end-systolic volume index; SVI, stroke volume index; EF, ejection fraction; C, control; N, 40 minutes after nifedipine administration.

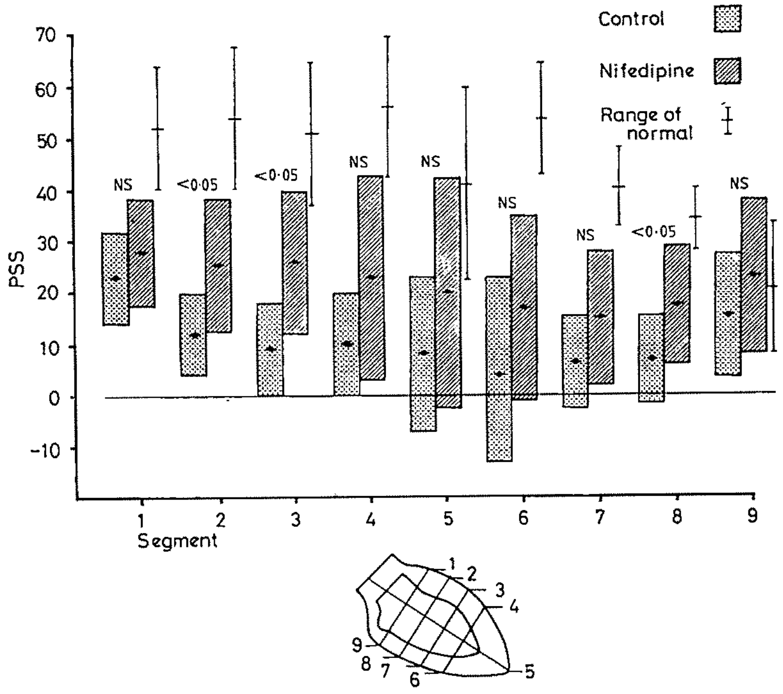

Fig. 3 Top: *Changes in percentage of systolic shortening (PSS) for nine segments considered, compared with normal values (mean ± SD).* Bottom: *Identification of nine segments on ventricular silhouette.*

Nifedipine exerts in vitro a pronounced relaxation on vascular smooth muscle,[18] and this finding was subsequently confirmed in studies undertaken in man.[9 16] It is likely, therefore, that afterload reduction, resulting from arteriolar vasodilatation, is responsible for the haemodynamic changes and the improvement in left ventricular performance observed in our patients. The fall in systemic vascular resistance was more pronounced in the patients with high initial resistance levels (Fig. 4) and this may suggest that nifedipine acts predominantly where arteriolar tone is higher. The effect of nifedipine on pulmonary vascular resistance is similar and consistent with this suggestion.

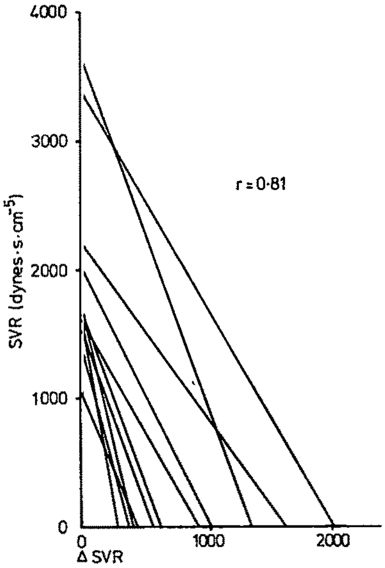

Fig. 4 *Fall in systemic vascular resistance (ΔSVR) compared with initial values (SVR) in 11 patients studied.*

A significant decrease took place only in the seven patients with high resistance (Fig. 1) and was well correlated with the initial resistance levels (Fig. 2). The decrease in right atrial pressure that occurred only in a few patients does not necessarily mean that nifedipine acts directly on preload, and it may be explained by the improvement in ventricular emptying which follows the reduction of arterial impedance. That nifedipine does not act on preload is supported by other data showing no venous pooling effect after the administration of the drug.[20]

Previous and present data indicate that nifedipine is an active afterload reducing agent. Since nifedipine, in vitro, exerts a negative inotropic effect, it is thus likely that the observed increase in ejection fraction and stroke volume is secondary to the afterload reduction and not a direct inotropic effect on the heart. Nifedipine has already been used to treat hypertensive emergencies.[16] Present data suggest that it can also be safely used to provide a rapid and distinct ventricular unloading in patients with left ventricular failure and raised systemic vascular resistance. There are still several problems, however, concerning the use of nifedipine as an alternative to vasodilator drugs currently used for the long-term treatment of heart failure.

Further studies are needed to document the duration of the acute haemodynamic effects in patients with heart failure. Previous observations in hypertensive patients showed a significant effect still persisting two hours after a 10 mg oral dose. Further studies, moreover, should determine whether the observed haemodynamic changes persist during long-term treatment and if any undesirable effects are associated with drug dosages higher than those used in the treatment of angina pectoris.

We thank Dr William McKenna for reviewing the manuscript.

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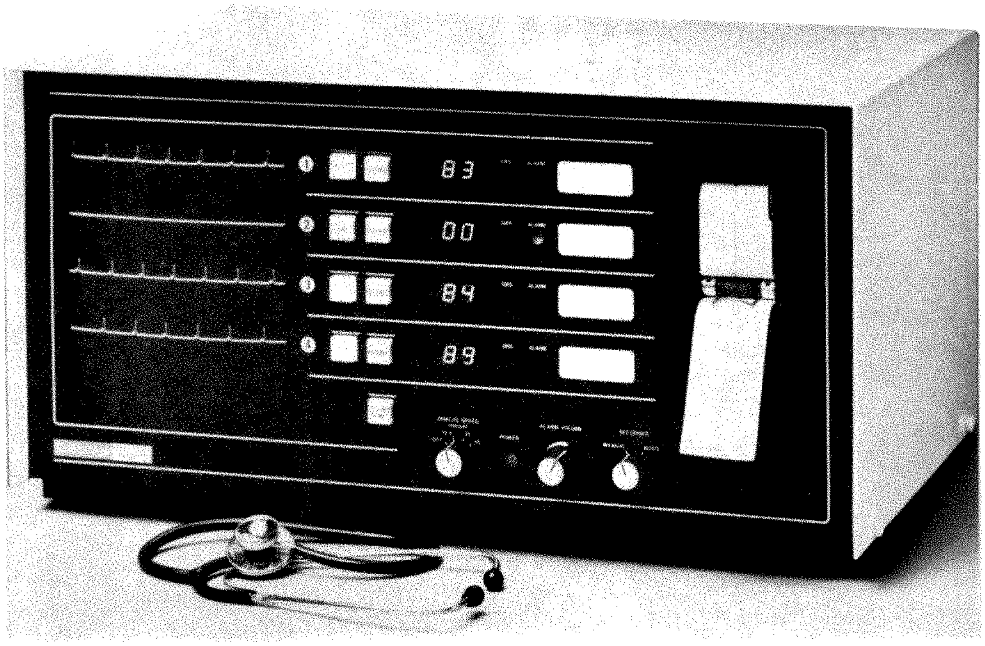

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Paroxysmal ventricular tachycardia during repeated 24-hour ambulatory electrocardiographic monitoring of postmyocardial infarction patients*

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SUMMARY Twenty-four hour ambulatory electrocardiographic tape recording was carried out four times within the first six months after an acute myocardial infarction in 100 consecutive patients below the age of 70 years. Sixty-four episodes of ventricular tachycardia were observed on 23 tapes recorded from 19 patients. Six episodes were accompanied by symptoms; syncope occurred twice. Ventricular tachycardia was rare during sleep, and occurred more commonly after discharge than in hospital. Forty-seven per cent of the episodes were 10 or more beats in length, and the maximum heart rate in each varied from 108 to 300/min. The heart rate immediately beforehand was 89/min ±15 (SD), and was not constant in any individual experiencing repeated attacks. Episodes, even longer ones, were not followed by significant tachycardia. Patients with ventricular tachycardia or ventricular fibrillation in the coronary care unit were significantly more likely to develop ventricular tachycardia later ($p < 0.05$), and ventricular tachycardia was more frequent after transmural than subendocardial infarction ($p < 0.05$). In hospital, the group with ventricular tachycardia was significantly more likely to have a sleeping heart rate of 80/min or more ($p < 0.05$). The mean prematurity index (RR′/QT) of the first complex of each episode of ventricular tachycardia was 1.41 ± 0.28 (SD) and no episode was triggered by the R of T phenomenon, which was seen 43 times. Four patients died suddenly in the six-month follow-up period; none had ventricular tachycardia, which was seen in two of the four patients who reinfarcted. The investigation shows that ventricular tachycardia occurs frequently during the first six months after a myocardial infarction, but it is usually self-limiting and asymptomatic, whether patients are or are not receiving antiarrhythmic treatment.

It is generally accepted that sudden death in patients with ischaemic heart disease results from ventricular fibrillation, and that electrical instability in the myocardium frequently precedes the fatal arrhythmia.[1] Arrhythmias in patients who have recently recovered from a myocardial infarction are of special interest, therefore, as these patients are prone to sudden death. Several investigations using electrocardiographic tape recordings over a period of hours during recovery from infarction showed that frequent ventricular extrasystoles, multifocal ventricular extrasystoles, and paired ventricular extrasystoles as well as ventricular tachycardia indicate a poor prognosis in this respect,[2-6] but another recent study did not support this.[7] More controversy has been added by the assertion that ventricular tachycardia in patients discharged from hospital after acute myocardial infarction[8] or in those with other heart diseases[9] is usually self-limiting, accompanied by few symptoms, and without any serious risk of progression to ventricular fibrillation.

The objects of the present investigation were to study the incidence of ventricular tachycardia during the first six months after acute myocardial infarction, to relate this back to the acute illness in an attempt to predict patients liable to develop ventricular tachycardia later, and to determine the prognosis of this arrhythmia.

Subjects and methods

The subjects were 100 consecutive patients, admitted after January 1978 to the coronary care unit of the Odense University Hospital, who had a

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* This investigation has been supported by a grant from The Danish Heart Foundation (Hjerteforeningen).

Received for publication 11 December 1979

proven acute myocardial infarction, were less than 70 years of age at the time of admission, and were discharged alive. All gave their informed consent to the investigation. Nine others complying with the above criteria were not studied; three refused, three lived too far away, two were employed in the hospital, and one suffered from catatonic schizophrenia. Each of the 100 patients underwent 24-hour electrocardiographic recordings during the later stages of their hospital stay as well as one, three, and six months after discharge.

The diagnosis of acute myocardial infarction was made using the criteria of the World Health Organization.[10] Continuous monitoring of the electrocardiogram in the coronary care unit used a frequency based alarm system, combined with surveillance of the oscilloscope by specially trained nurses. The electrocardiograms were continuously recorded on tape and played back in cases where difficulty in identification of arrhythmias occurred. The arrhythmias observed were recorded on a special form.

On one of the last days before discharge from hospital, as well as one, three, and six months after discharge patients were examined and their drug regimen noted. The resting 12-lead electrocardiogram was recorded and a 24-hour tape recording obtained using a Medilog tape recorder (two leads). Analysis of the 24-hour tapes was carried out by a Pathfinder High Speed Electrocardiogram Analyser at 60 times real time using the automatic analysis facility of the instrument combined with continuous surveillance of the electrocardiogram on the oscilloscope. All paired ventricular extrasystoles, R on T extrasystoles, and episodes of ventricular tachycardia were recorded on paper at normal speed for closer inspection and documentation. The total number of ventricular extrasystoles was counted using a digital counter connected with the logic output of the analyser.

Each tape was divided into four periods of six hours. The mean heart rate, the number of ventricular extrasystoles, the number of paired ventricular extrasystoles, the number of R on T ventricular extrasystoles, and the number of episodes of ventricular tachycardia were noted for each six-hour period. The heart rate immediately before and after episodes of ventricular tachycardia was measured over three normal beats.

Ventricular tachycardia was defined as three or more consecutive ventricular extrasystoles at a rate of 100 beats/minute or more, and R on T ventricular extrasystoles as those with an RR'/QT ratio of less than one. The patients continued their usual daily activities during the period of monitoring; no change was made in their drugs.

During the follow-up period of six months, five patients died, four from sudden cardiac death with symptoms of less than one hour's duration, all before the first ambulatory monitoring, and the fifth from a cerebrovascular accident six months after the attack of myocardial infarction. One of the 100 patients moved away and did not have the final 24-hour tape recording.

STATISTICS

Fisher's exact test and Student's t test were used. The significance level was 5 per cent.

Results

In a total of 386 24-hour recordings, 64 episodes of ventricular tachycardia were observed on 23 tapes from 19 patients. The arrhythmia was self-limiting in all cases, and did not progress to ventricular fibrillation. Table 1 shows the time of relation of these episodes. A single episode was observed on 16 tapes, two on four tapes, and seven, 12, and 20 episodes, respectively, on one tape each.

The number of beats in each episode of ventricular tachycardia can be seen in Fig. 1; in 16 per cent they consisted of three beats only, and in 47 per cent of 10 or more. The mean maximum heart rate during ventricular tachycardia (Fig. 2) was 179 ± 35 (SD) per minute (range 108 to 300). The mean heart rate immediately before ventricular tachycardia was 89 ± 15 (Fig. 3), while the mean heart rate during the six-hour period in which it occurred was 75 ± 13. This difference is statistically significant ($p < 0·001$). Two episodes occurred during sleep between midnight and 6 am, and 13 between 6 pm and 12 midnight. In two cases ventricular tachycardia was accompanied by syncope and in four by dizziness.

Table 1 *Timing of ventricular tachycardia in relation to acute myocardial infarction*

	Late hospital phase (No. = 100)	*One month after AMI (No. = 96)*	*Three months after AMI (No. = 96)*	*Six months after AMI (No. = 96)*
No. of tapes with ventricular tachycardia	3	8	5	7
No. of episodes of ventricular tachycardia	3	10	27	24

AMI, acute myocardial infarction. No., number of tape recordings.

Ventricular tachycardia was not followed by an increase in heart rate as compensation for a presumed drop in cardiac output; immediately beforehand the heart rate was 89±15, while immediately afterwards it was 88±12. This difference is not statistically significant. Longer episodes of ventricular tachycardia did not differ from shorter ones in this aspect.

Forty-three instances of R on T extrasystoles were seen in nine patients, and, of these, two had episodes of ventricular tachycardia on the same tape, but in no case was the prematurity index (RR′/QT) of the first extrasystoles of any episode of ventricular tachycardia less than one (Fig. 4), and the mean index was 1·41±0·28 (range 1·00 to 2·53).

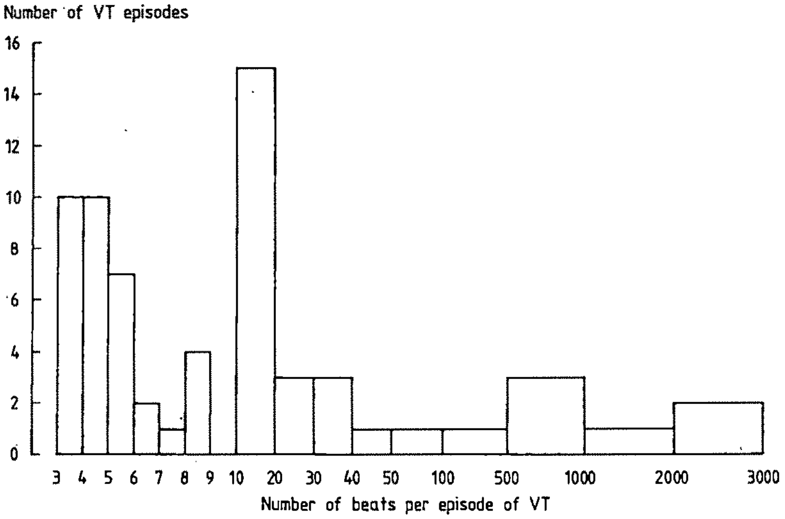

Fig. 1 *The number of beats in each episode of ventricular tachycardia.*

Table 2 compares the 19 patients who experienced one or more episodes of ventricular tachycardia and the 81 patients who did not. There was no significant difference in age, sex, cardiac history, or presence of risk factors. Ventricular tachycardia occurred significantly more frequently after transmural than after subendocardial infarction ($p < 0{\cdot}05$). It was also more frequent after inferior than after anterior infarction, but not significantly. In the coronary care unit, patients later developing ventricular tachycardia were more likely to have had ventricular extrasystoles (NS), and ventricular tachycardia, and ventricular fibrillation (both $p < 0{\cdot}05$). The incidence of cardiac failure (using the criteria of Killip and Kimbal)[11] or of massive infarction (suggested by a maximum LDH value of more than 3000 units per litre) did not differ significantly between the two groups. During the 24-hour electrocardiographic monitoring in hospital a heart rate of 80/min or more during sleep (midnight to 6 am) was significantly more frequent in the group with ventricular tachycardia ($p < 0{\cdot}05$). At this point 10 of these 19 patients were receiving digoxin and/or antiarrhythmic agents compared with 46 of the remaining 81.

At the time of recording, of the 23 tapes showing ventricular tachycardia five of the patients concerned were being treated with digoxin, three with beta-blockers, and two with both. The proportion of the remaining 363 tapes recorded while patients were taking these drugs was not significantly different. For quinidine and procainamide the figures were zero and 31 recordings, respectively. The most frequent indication for beta blockers was angina pectoris and, therefore, the doses given were higher

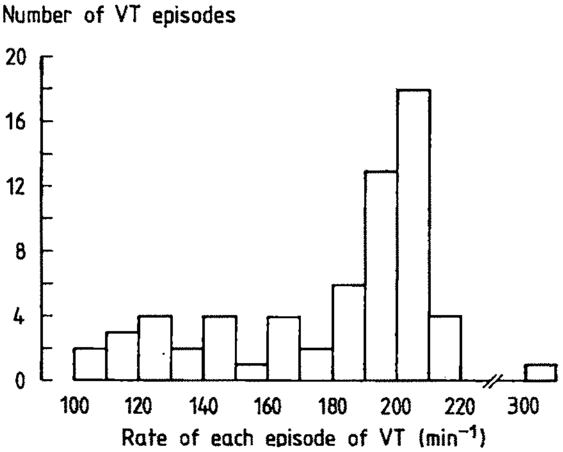

Fig. 2 *The maximum heart rate of each episode of ventricular tachycardia.*

than those normally used for antiarrhythmic treatment (80 to 320 mg propranolol per day); the doses of quinidine and procainamide were 1·2 to 1·6, and 3 g per day, respectively. In summary, digoxin and/or antiarrhythmic agents were being given during 10 out of 23 of the recordings showing ventricular tachycardia as compared with 182 of 363 of the remainder. These proportions are not significantly different.

Four cases of sudden cardiac death occurred during the period of follow-up of six months, all with symptoms lasting less than one hour. In the coronary care unit one of these patients had had ventricular fibrillation, one ventricular tachycardia, one paired ventricular extrasystoles, and one frequent ventricular extrasystoles. During 24-hour monitoring before discharge from hospital two had had frequent and multifocal ventricular extrasystoles and the other two isolated unifocal ventricular extrasystoles.

Four of the patients had a further myocardial infarction, and these occurred between 13 and 151 days after the original one. In the coronary care unit during the first admission one of these patients had had paired ventricular extrasystoles, two frequent ventricular extrasystoles, and the last patient isolated ventricular extrasystoles. During the 24 hours of monitoring in the hospital, two of these patients had had ventricular tachycardia, one frequent ventricular extrasystoles, and one isolated unifocal ventricular extrasystoles.

Discussion

This study shows that ventricular tachycardia occurs frequently during the first months after acute myocardial infarction. The differing incidence in previously published reports may be the result of variations in patient selection, in definition of ventricular tachycardia, in the duration of electrocardiographic monitoring and in the technique of analysis. During the later stages of the hospital

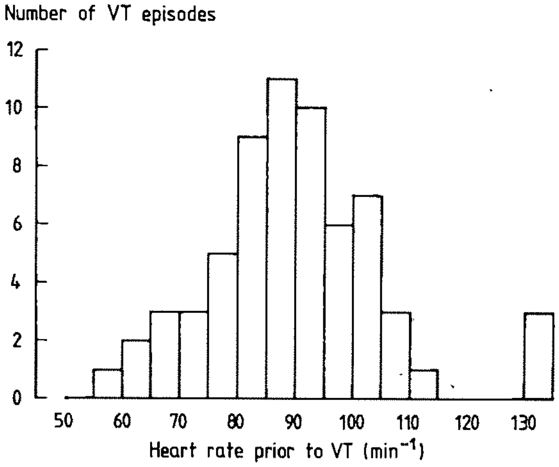

Fig. 3 *The heart rate immediately before each episode of ventricular tachycardia.*

Table 2 *Clinical characteristics of 100 consecutive postmyocardial infarction patients, with and without ventricular tachycardia, during 24 hours of ambulatory electrocardiographic monitoring*

Clinical	*Ventricular tachycardia present (No.=19)*	*Ventricular tachycardia absent (No.=81)*	*p value*
Previous medical history			
Stable angina	5	25	
Unstable angina	5	18	
Myocardial infarction	4	18	
Heart failure	3	16	
Hypertension	4	23	
Smoking	14	47	
Age (y) (mean ± SD)	60 ±8	58 ±8	
Men	17	63	
Site of infarction			
Anterior	5	39	
Inferior	10	24	
Anterior + inferior	3	12	
Unknown	1	6	
Type of infarction			
Transmural	17	51	$<0\cdot05$
Data from CCU			
First systolic BT < 100 mmHg	2	6	
Killip class 2–4	14	59	
Cardiothoracic ratio ⩾0·50	10	54	
Maximum LDH > 3000 U/l	3	12	
Ventricular extrasystoles present	18	62	
Ventricular tachycardia present	7	12	$<0\cdot05$
Ventricular fibrillation present	5	7	$<0\cdot05$
Status on discharge from hospital			
Resting electrocardiogram			
Heart rate (mean ± SD)	74 ±13	76 ±14	
Ventricular extrasystoles	2	11	
ST elevation ⩾1 mm	6	36	
24-hour tape recording			
Heart rate (mean ± SD)	76 ±11	76 ±12	
Heart rate during sleep (mean ± SD)	71 ±12	69 ±11	
Heart rate > 80/min during sleep	7	11	$<0\cdot05$
Ventricular extrasystoles present	11	73	
Ventricular extrasystoles present during sleep	15	55	
Ventricular extrasystoles/h (mean > 10)	4	15	
Ventricular extrasystoles/h (mean > 1)	13	38	
Ventricular extrasystoles/h during sleep (mean > 1)	12	31	
Multifocal ventricular extrasystoles	4	19	
Paired ventricular extrasystoles	2	9	
Ventricular bigeminy	3	12	
Digoxin or antiarrhythmic treatment	10	46	

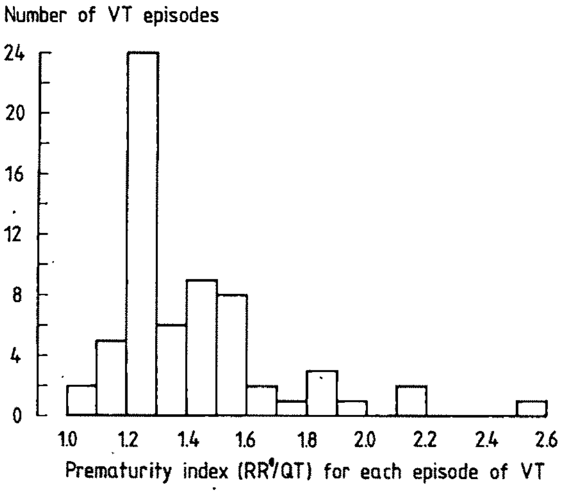

Fig. 4 *The prematurity of the ventricular extrasystoles starting each episode of ventricular tachycardia.*

stay ventricular tachycardia was found in 3 per cent of the patients in the present investigation, while the incidence in studies using the exercise electrocardiogram during the early stages of recovery from acute myocardial infarction is stated to be between 0·5 and 1 per cent,[12 13] and 1 to 6 per cent using tape recording.[2–4 6] Between one and six months after infarction in the present study ventricular tachycardia was observed in an additional 16 per cent of the patients during a total of 72 hours of monitoring each, but in other studies the incidence has varied from 1 to 20 per cent, single or repeated periods of monitoring for between six and 24 hours being used.[2 4 6 14–16] In two of these investigations in which monitoring was repeated and included the first three months after infarction, ventricular tachycardia was observed in 10 to 15 per cent of the patients.[2 15]

The R on T phenomenon was observed in 9 per cent of the patients but, as others have found, ventricular tachycardia was not usually triggered by such extrasystoles.[8 9]

In Table 3 the present study is compared with those two others with respect to the heart rate immediately before ventricular tachycardia and the prematurity index. There is considerable agreement and this despite the fact that the investigation of Winkle *et al.*[9] included patients both with and without cardiac disease. However, our patients had much longer episodes of ventricular tachycardia, approximately half of these being 10 or more ventricular extrasystoles in length. The greater electrical instability of the myocardium during the first months after a myocardial infarction may account for this difference as this period was not included in the other two studies, though the longer episodes of ventricular tachycardia were in fact evenly distributed, did not occur at any special time of the day, and were not preceded by a heart rate which differed from that of the other episodes. Ventricular tachycardia occurred rarely during the night or in the evening, which is in contrast to the findings of others,[17] but in some studies a reduction in the number of ventricular extrasystoles during sleep has been found.[18 19]

The mean heart rate immediately before episodes of ventricular tachycardia was relatively rapid, and was significantly higher than the mean for the six-hour period in which they occurred. Bradycardia, therefore, did not appear to be of importance in triggering ventricular tachycardia as has been described in the acute stage of the infarction.[20]

Exercise studies of individual patients have shown that ventricular tachycardia occurs at the same heart rate both before and during antiarrhythmic treatment,[21] but this was not so with those of our patients who experienced several episodes. Thus, in a patient who had ventricular tachycardia 20 times within a single 24-hour period, the heart rate beforehand varied between 79 and 130 beats/min.

Since ventricular tachycardia tends to follow a sinus tachycardia, beta blockers may prevent

Table 3 *Comparison with previous studies*

Authors	*Patients*	*No. of patients with ventricular tachycardia*	*No. of episodes of ventricular tachycardia*	*Heart rate/min before ventricular tachycardia (mean ± SD)*	*Peak ventricular tachycardia rate/min (mean ± SD)*	*No. of ventricular tachycardia with three ventricular extrasystoles* (%)	*Prematurity index (mean ± SD)*
Winkle *et al.*[9]	Various heart diseases	23	94	83 ±17	148 ±26	49	1·36 ±0·27
Anderson *et al.*)[8]	Four to 48 months after acute myocardial infarction	66	199	87 ±19	152 ±24	47	1·49 ±0·37
Present study	Nought to six months after acute myocardial infarction	19	64	89 ±15	179 ±35	18	1·41 ±0·28

sudden cardiac death by preventing the latter, though in our study they appeared to exert no protective effect. However, ventricular tachycardia was commoner after inferior infarction, so it is possible that beta blockers exert a greater antiarrhythmic effect in anterior infarction. This would be in agreement with the multicentre international practolol study,[22] but further investigation is needed on this point.

The failure of heart rate after an episode of ventricular tachycardia to increase in compensation for the reduction in cardiac output during the arrhythmia is remarkable. Even the longest lasting episodes were not followed by any significant increase. It is also remarkable that only six of 64 episodes of ventricular tachycardia produced significant symptoms.

The connection between ventricular tachycardia and fibrillation in the coronary care unit and the occurrence of ventricular tachycardia later has previously been confirmed by some,[7 23] but only partly by others.[3 4 8] The association with transmural rather than subendocardial infarction may be because the former judged by the maximum increase in serum enzymes tends to be larger, but size does not explain the higher incidence of ventricular tachycardia in inferior as compared with anterior infarctions.

The study shows that of all indices measured in the late hospital phase only the heart rate during sleep is helpful in forecasting the likelihood of ventricular tachycardia in the first six months after myocardial infarction, but it is impossible, even so, to do this with any certainty. The study also shows, in agreement with others,[7 8] that ventricular tachycardia does not necessarily carry a poor prognosis, is frequently self-limiting even in the absence of antiarrhythmia treatment, is not very likely to proceed to ventricular fibrillation, and rarely produces symptoms.

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Br Heart J 1980; **43:** 454–7

Lightning and the heart

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SUMMARY Two patients sustained lightning-induced myocardial necrosis and had clinical evidence of myocardial injury. In the first case, clinically more severely affected, the electrocardiographic changes simulated acute inferior myocardial infarction while in the second case only mild non-specific ST and T wave changes were seen. The presence of cardiac muscle creatine kinase isoenzyme confirmed that these non-specific changes also reflected myocardial necrosis. Resting thallium-201 myocardial imaging in the first case showed normal perfusion. In both cases there was complete clinical and electrocardiographic recovery.

Lightning injuries may involve almost any organ. Myocardial necrosis after lightning injury has been demonstrated at necropsy.[1–3] During life, however, this has only been inferred from electrocardiography and vonventional serum cardiac enzyme studies. The extent to which the raised serum enzymes reflect myocardial damage, so far as we know, has not previously been reported. We describe two patients in whom lightning injury involved the heart and in whom cardiac creatine kinase (CK) isoenzyme was assayed. In the first, electrocardiographic abnormalities of acute inferior myocardial necrosis were present but serum cardiac CK was absent and thallium-201 myocardial imaging showed normal perfusion of the inferior surface of the heart. In the second case despite only transient electrocardiographic changes the cardiac muscle CK isoenzyme was raised.

Case histories

On 4 June 1978 lightning struck a group of three doctors with their families enjoying a Saturday afternoon at a leisure park. They had been caught in a thunderstorm and were sheltering under a tree. Of the five adults and three children in the group only three adults were injured.

The two most seriously affected arrived in the casualty department within 30 minutes.

CASE 1

A 41-year-old man had been holding an umbrella in his right hand and a baby in his left arm. The baby was unhurt. His first memory after the event was of complete paralysis of both legs and right arm followed by gasping for breath. During the following 30 minutes he regained the power in his limbs but developed a severe burning pain in his right arm and shoulder. He had no history of heart disease nor had he ever had an electrocardiogram recorded. There were extensive first degree burns of his right arm and shoulder together with singed hairs on the left leg and right chest. The remains of the corresponding part of his shirt are shown in Fig. 1. There was an exit burn on the lateral aspect of the right foot approximately 1 mm in diameter. A corresponding hole had been burnt in the right shoe (Fig. 2). The blood pressure was 110/70 mmHg and there were no signs of cardiac failure. Tone, power, and reflexes were reduced in both legs; plantar responses were flexor. There was complete destruction of the tympanic membrane on the right side with corresponding loss of air conduction. Over the six hours after admission his systolic blood pressure fell progressively to 80 mmHg, but this returned to normal after four hours.

Serial hydroxybutyrate dehydrogenase (SHBD), total CK, alanine transaminase (ALT) levels (Table), and electrocardiograms (Fig. 3) were performed. Thallium-201 resting myocardial imaging at 19 days showed normal perfusion of the inferior surface of the heart, despite the electrocardiographic abnormalities. He made a good recovery, his burns healing without scarring. At three months only the Q waves persisted on the electrocardiogram and these were less than 2 mm in amplitude and less than 0·04 seconds in duration. Myringoplasty will be performed in due course.

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Received for publication 3 August 1979

CASE 2

A 43-year-old man had severe, tight, central chest pain together with shortness of breath. His first memory on 'waking up' was that he was totally paralysed. As the paralysis disappeared he developed paraesthesiae initially in the right arm and then in both legs. The chest pain developed some minutes later. Again, there was no relevant past history. There were singed hairs over the right arm and leg and an exit burn on the lateral aspect of the right foot, approximately 1 mm in diameter. The blood pressure was 90/60 mmHg rising to 110/70 mmHg after 15 minutes. There was no neurological deficit. The electrocardiogram at one hour showed non-specific ST-T wave changes in the anterolateral leads (Fig. 3). These changes had resolved after 24 hours. Serial enzyme studies are shown in the Table. He made a rapid recovery and was discharged after five days complaining only of mild aches and pains. A week later he still had some weakness of grip and dorsiflexion of the foot on the left, with an extensor plantar response on the left.

Discussion

The atmospheric conditions that give rise to lightning are now well known.[3–5] Lightning may cause current to flow by direct strike, side flash, or step voltage, depending on local circumstances. Side flash occurs when a direct strike hits a conductor of high resistance and represents a pathway of lower resistance. The step voltage effect is caused by a potential difference being set up between the feet.[4] The mechanisms by which injuries are produced include (a) electrical burns; (b) interference with the electrical status of neuro-

Fig. 1 *Shirt from case 1.*

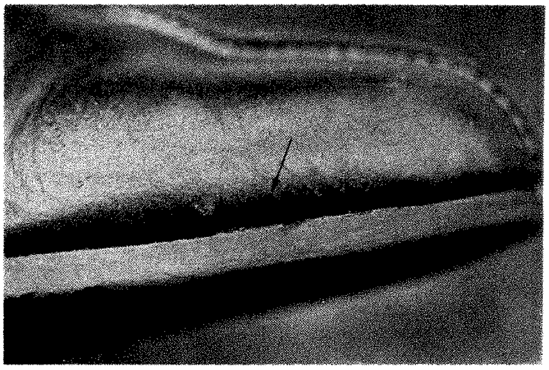

Fig 2. *Right shoe from case 1 showing exit burn hole.*

Table *Serial serum enzyme studies*

	Investigations	*Approximate time after injury*					
		1 h	*24 h*	*48 h*	*72 h*	*4 d*	*9 d*
Case 1	SHBD (IU/l)	577	268	214			133
	Total CK (IU/l)	248	701	533			400
	CK isoenzymes:						
	Skeletal muscle	+ve		+ve	+ve		
	Cardiac muscle	−ve		−ve	−ve		
	Brain	−ve		−ve	−ve		
	ALT (IU/l)		673		314		89
Case 2	SHBD (IU/l)		166	207		204	
	Total CK (IU/l)		1752	832		431	
	CK isoenzymes:						
	Skeletal muscle		+ve			+ve	
	Cardiac muscle		+ve			−ve	
	Brain		−ve			−ve	
	ALT (IU/l)		58			54	

Reference values: Hydroxybutyrate dehydrogenase (SHBD) = < 230 IU/l.
Total creatine kinase (CK) = 20 to 170 IU/l.
Alanine transaminase (ALT) = < 30 IU/l.

muscular cells (including the effects of muscular spasm and cardiac arrhythmias); and (c) blast injuries.

In both our patients the findings were compatible with a combination of step voltage and side flash injuries. The step voltage effect characteristically caused paralysis and weakness of the legs. The more serious injuries in our first patient were probably the result of a side flash rather than a direct strike. The group was sheltering under a large tree and was within 15 feet of a railway line. A furrow had been produced in the ground by the lightning, linking the group with the railway line. The likely sequence of events was that the lightning hit the nearby tree and took the path of least resistance by side flashing to the umbrella, thence through the patient, and finally across the ground to the railway line.

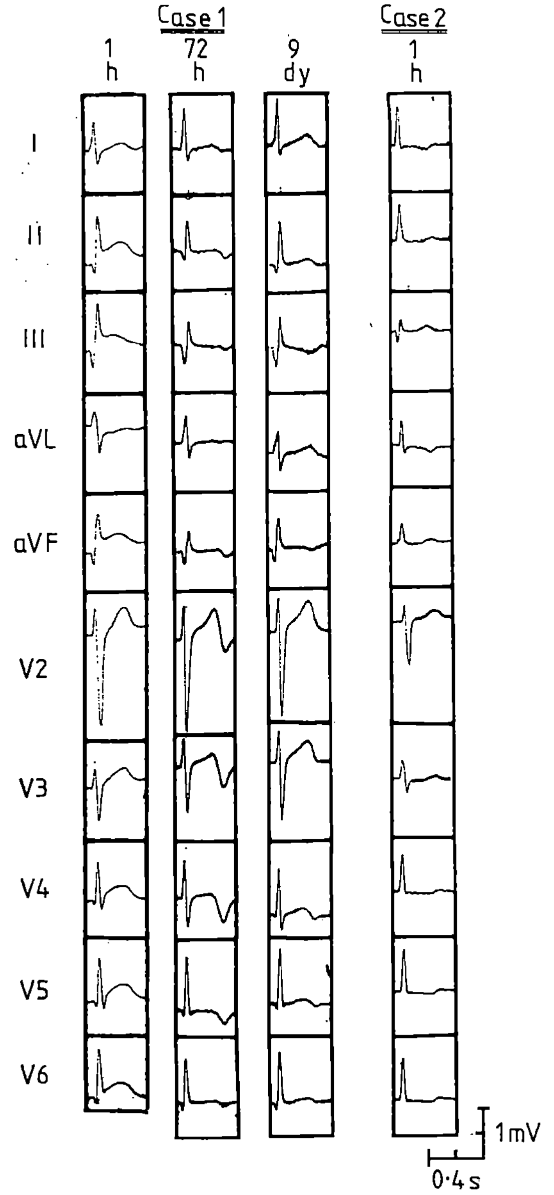

Fig. 3 *Serial electrocardiograms from case 1 and initial electrocardiogram from case 2.*

The burns and singed hairs suggest that the major pathway taken by the lightning was superficial in both patients, perhaps partly because of wet clothes. The appearances in the tympanic membrane were those of an electric burn, which is not in keeping with the usual finding of blast injury.[6] The late neurological sequelae in case 2 suggest pyramidal tract damage but the significance of this is not clear, though delayed neurological effects have recently been attributed to oedema of the spinal cord.[7]

In the first patient the clinical course and serial changes in the inferior electrocardiographic leads suggest that transmural myocardial necrosis occurred. In addition, the ST-T wave changes in the anterolateral leads suggest that diffuse myocardial injury may also have occurred. The absence of cardiac CK isoenzyme in the presence of myocardial necrosis could be explained by the more rapid clearance of the cardiac relative to the skeletal muscle isoenzyme,[8] the assay not being performed at 24 hours on this patient. The normal thallium imaging suggests that the necrosis was not the result of infarction. However, myocardial imaging is a qualitative study dependent on the demonstration of relative differences of radionuclide uptake. Hence, particularly in situations where there are diffuse changes on the electrocardiogram, false negative studies can occur.[9]

In the second patient the early clinical course and ST-T wave changes, though non-specific in themselves, are confirmatory evidence that the cardiac CK isoenzyme represents myocardial necrosis.

It is clear from our cases that while myocardial necrosis resulting from lightning injury may produce electrocardiographic abnormalities simulating acute myocardial infarction, it may also produce short-lived non-specific ST-T wave changes. Further, we suggest that in this context where skeletal muscle damage almost invariably occurs, total CK levels may be misleading.

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Br Heart J 1980; **43:** 458–62

Electrophysiological manifestations of non-penetrating cardiac trauma

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SUMMARY Electrophysiological disturbances were observed in four cases of non-penetrating cardiac trauma. Ventricular tachycardia occurred both as an early and late complication in three, responding to medical treatment in two; it was cured by cryoablation in the other case. The fourth patient developed an isolated conduction defect associated with anteroseptal myocardial infarction, the coronary arteries and left ventricular function being normal.

Non-penetrating injuries to the chest may affect the heart in several ways, including electrophysiological disturbance, in particular cardiac arrhythmia.[1 2] Ventricular tachycardia poses a particular problem as it is usually incapacitating and may prove fatal. Though medications may control these arrhythmias, pacing or surgery may be required.[3] We report the electrophysiological consequences of non-penetrating trauma to the heart in four patients: three had ventricular tachycardia including one with a resistant arrhythmia that required operation; the remaining patient developed an isolated conduction defect.

Received for publication 12 September 1979

Case 1

A 25-year-old man had suffered from recurrent palpitation associated with chest pain and dizziness for five years. During an episode an electrocardiogram disclosed ventricular tachycardia (Fig. 1); after cardioversion there were changes consistent with old anterior infarction (Fig. 2). At the age of 7 years a horse had kicked his chest, throwing him 20 metres. Examination and routine investigations including chest x-ray were normal. Left ventricular angiography showed an apical aneurysm (Fig. 3), but the coronary arteries were normal. Despite propranolol, verapamil, and disopyramide, the

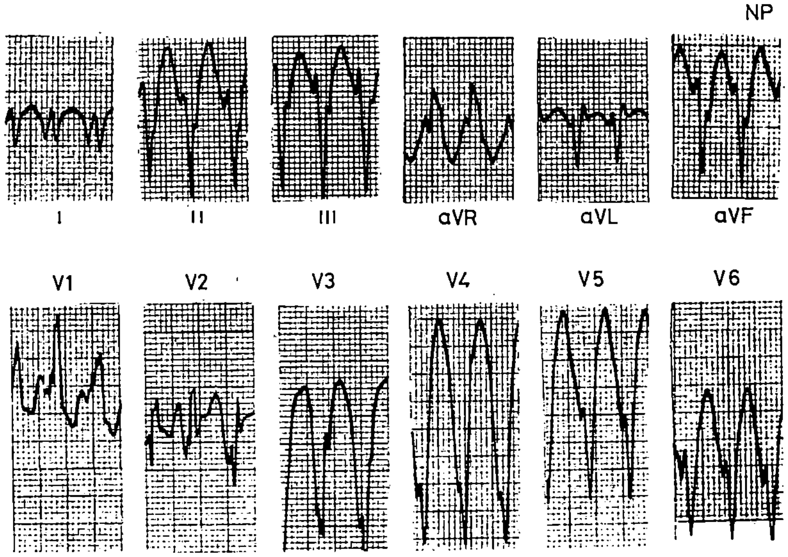

Fig. 1 *Case 1: electrocardiogram during tachycardia.*

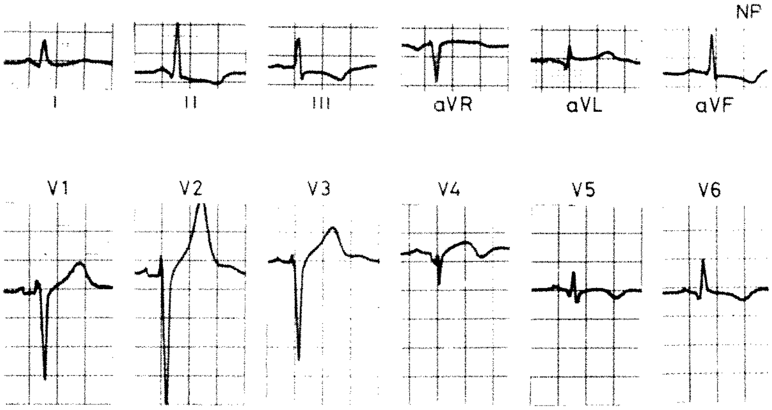

Fig. 2 *Case 1: electrocardiogram in sinus rhythm showing changes of old anterior infarction.*

tachycardia recurred. An electrophysiological study[4] disclosed no abnormality nor could tachycardia be induced, but pacing was not attempted from the left ventricle.

At operation, a small ventricular aneurysm was found adjacent to the anterior descending branch of the left coronary artery and related to the second diagonal branch; apart from a few fibrous adhesions the heart and coronary arteries were normal. On epicardial mapping with hand-held bipolar and tripolar electrodes the signals, together with atrial and ventricular reference electrograms, were recorded simultaneously with leads I, II, III, and aVF, using an Elema Mingograf 81 direct writing recorder. During sinus rhythm activation was abnormal in the region of the aneurysm: epicardial potentials occurred up to 130 ms after the reference ventricular electrogram and well after the QRS complex (Fig. 4A). At the lower edge of the aneurysm the initial depolarisation during the QRS complex (Fig. 4B) was followed by an afterpotential[5] and a subsequent ventricular extrasystole with the same configuration as seen during ventricular tachycardia. The relation between the reference and local potentials during the extrasystole was identical to that during tachycardia.

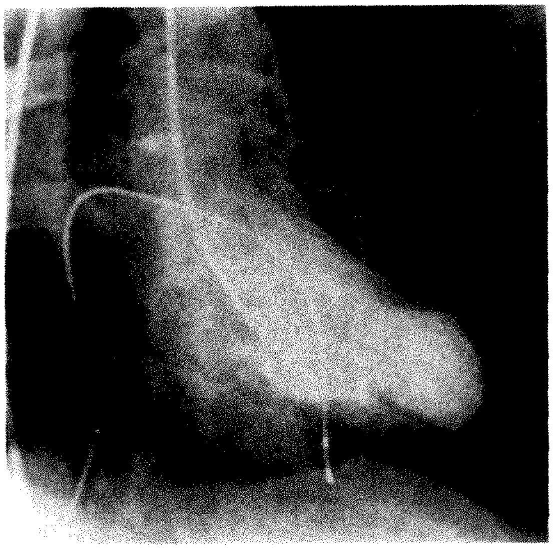

Fig. 3 *Case 1: left ventricular angiogram (right anterior oblique) showing an anteroapical aneurysm; there is a pacing wire in the right ventricle.*

Ventricular tachycardia occurred spontaneously or could be initiated by two ventricular extrastimuli delivered through the ventricular reference electrode. Epicardial activation was earliest along the inferior border of the aneurysm and preceded the onset of the QRS complex by 20 ms (Fig. 4C); activation spread across the epicardial surface towards the base of the heart, again being slow along the left border of the aneurysm (Fig. 4D).

The left and inferior margin of the aneurysm was cryoablated[6] and though conduction remained slow over the centre of the aneurysm during sinus rhythm, it proved impossible to reinitiate the tachycardia. The aneurysm was then plicated. The postoperative course was uncomplicated and he has been free from palpitation for two years.

Case 2

A 31-year-old male electrician developed chest pain and shortness of breath immediately after lifting an extremely heavy electrical cable (200 kg) and carrying it 200 metres. He was admitted to hospital and found to have ventricular tachycardia at a rate of 160 a minute. Intravenous practolol and oral digoxin had no immediate effect and the arrhythmia stopped after 23 hours. The subsequent

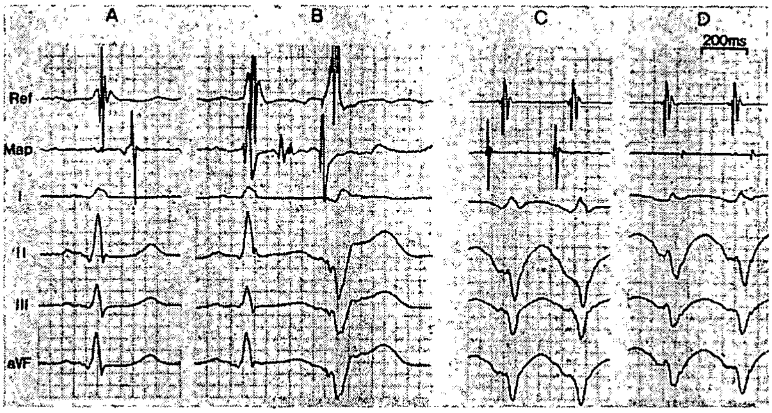

Fig. 4 *Case 1 : Examples of the activation sequences recorded during epicardial mapping, paper speed 100 mm/s. Each panel shows an epicardial electrogram recorded from a fixed reference point 2 cm cranial to the aneurysm (Ref), an epicardial electrogram recorded with the moveable electrode (Map), and leads I, II, III, and aVF.* (A) *Sinus rhythm, Map recorded from the centre of the aneurysm. Slow conduction is shown by the delayed local electrogram after the QRS.* (B) *Sinus rhythm, Map recorded from the lower border of the aneurysm. A local electrogram during the narrow QRS complex is followed by a low amplitude afterpotential and a third electrogram at the onset of a ventricular extrasystole which has a similar QRS morphology to that seen during ventricular tachycardia.* (C) *Map during ventricular tachycardia showing early local electrograms from the area of earliest epicardial activation, close to the lower pole of the aneurysm.* (D) *Map during ventricular tachycardia showing delayed local electrogram from the area of latest epicardial activation, at the left upper border of the aneurysm.*

electrocardiogram in sinus rhythm showed transient ST and T wave abnormalities in the inferior leads. Over the next six months he continued to suffer from tachycardia which always ceased spontaneously. He was admitted to the Hammersmith Hospital for further investigation. There were no cardiac abnormalities on examination and the resting electrocardiogram was normal, with a normal QTc interval and no abnormalities of repolarisation or evidence of ventricular hypertrophy. Chest *x*-ray and echocardiogram were both normal. Intracardiac electrography demonstrated normal atrioventricular nodal function both anterogradely and retrogradely, with no evidence of an accessory pathway or of atrioventricular nodal re-entry. On slow release quinidine (Kinidin Durules) he was free from tachycardia for two years so treatment was stopped and he has remained asymptomatic for the subsequent two years.

Case 3

A 46-year-old man had been completely well until the age of 31 when he developed a severe constricting chest pain while lifting a heavy weight. An electrocardiogram recorded three days later showed inferior myocardial infarction. He remained well until three years later when he was admitted to hospital with palpitation and shortness of breath but the electrocardiogram showed sinus rhythm. He then remained asymptomatic until one year before referral when he developed recurrent paroxysmal ventricular tachycardia. Though termination was often spontaneous, cardioversion was required 13 times in that year; there was no response to various prophylactic agents (quinidine, procainamide, disopyramide, digoxin, and beta-receptor antagonists). On admission he looked fit and had no clinical abnormalities. The resting electrocardiogram showed old inferior infarction; chest *x*-ray was normal. Echocardiogram showed an isovolumic contraction abnormality and the posterior wall of the left ventricle was hypokinetic. Angiography showed conspicuous inferior and apical dyskinesia with normal coronary arteries. On amiodarone (200 mg/day) he has been completely free from palpitation for two years.

Case 4

A fit 31-year-old male engineer had normal routine electrocardiograms performed for his employment on oil rigs, including a tracing in May 1977 (Fig. 5A). In June 1977 a steel plate fell on to his chest and he lost consciousness briefly. Electrocardiograms recorded 10 days after the accident, and subsequently, have consistently shown left axis deviation and loss of R waves in the anterior chest leads consistent with anterior myocardial infarction (Fig. 5B). Physical examination was normal and coronary arteriography and left ventricular angiography performed one year after the accident were likewise normal. He remains free of symptoms.

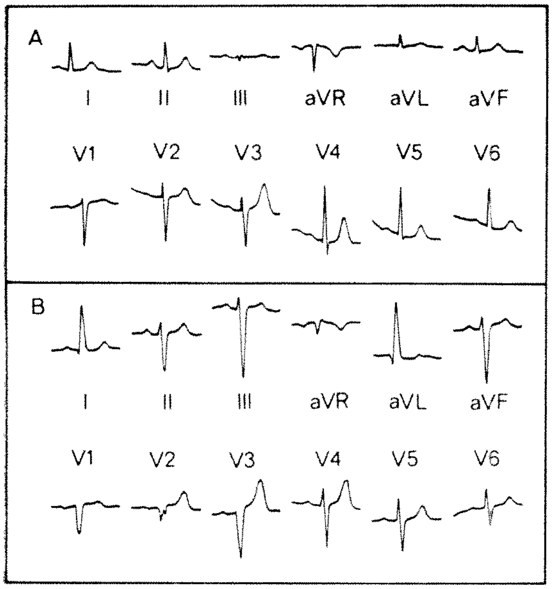

Fig. 5 *Electrocardiograms, case 4:* (A) *one month before injury: normal tracing;* (B) *10 days after injury there is left axis deviation as well as loss of R waves in the anterior chest leads.*

Discussion

Several mechanisms may be responsible for cardiac damage by non-penetrating trauma to the chest, including sudden acceleration or deceleration, direct compression by the sternum, or sudden increase in intrathoracic pressure[7]; the last seems applicable to cases 2 and 3. It can be impossible to distinguish between myocardial contusion and direct injury to a coronary artery. A wide variety of electrophysiological manifestations have been seen hours, months, or even years after the injury, including complete heart block and supraventricular and ventricular tachycardia.[8–10] Ventricular tachycardia is the most dramatic consequence and may result in syncope or even death; unfortunately, its treatment is often difficult and though there are now many useful antiarrhythmic agents, alternative forms of treatment may occasionally be needed.[5 11 12]

Acute myocardial infarction with subsequent development of a left ventricular aneurysm, as in case 1, is a well-recognised consequence of non-penetrating trauma to the chest.[13 14] Coronary arteriography has only rarely been performed after traumatic myocardial infarction, the coronary arteries usually being normal; as mentioned, it is unclear whether the infarct results from myocardial contusion or from direct injury to a coronary artery which then recanalises.[7 15] The long interval between the trauma and the development of the tachycardia in cases 1 and 3 is noteworthy.

We could not induce tachycardia during the electrophysiological investigation in case 1; a pacing electrode was not inserted into the left ventricle and because of the origin of the tachycardia close to the aneurysm, the right ventricular electrode was almost certainly too distant to allow us to demonstrate the features later seen at intraoperative mapping. At operation re-entrant tachycardia could be provoked from the left border of the aneurysm, with slowing of conduction between normal and abnormal myocardium which could produce changes in refractoriness. At operation it was not feasible to examine the response of the delayed afterpotential to critically timed premature ventricular beats or to assess the pattern of intramyocardial conduction with plunge electrodes.

The successful response to cryoablation after epicardial mapping emphasises the potential value of this approach to the treatment of refractory ventricular tachycardia. This emerges from observations that long-term survivors who had undergone aneurysmectomy for recurrent ventricular tachycardia relapsed after operation when epicardial mapping and cryoablation were not performed[16]; the arrhythmias might have persisted because the initiating site located in the margin of the aneurysm was not destroyed.[16 17] We believe that this is the first occasion in which cryoablation has been used for the treatment of this form of tachycardia. However, medical management may well succeed (cases 2 and 3).

In case 4 the development of electrocardiographic changes consistent with acute myocardial infarction and left axis deviation after chest trauma poses several questions, and raises medicolegal aspects. Left axis deviation in this context implies a disturbance of conduction in the left bundle-branch, perhaps by the effects of contusion. Despite the normal coronary arteries and left ventricular function, it is possible that further electrophysiological manifestations may appear later, including a greater degree of heart block[8] or, as in case 1, ventricular tachycardia, even without an aneurysm.[5] With greater awareness of the possible electrophysiological effects of injury to the heart, other cases similar to ours will be recognised, and a history of trauma to the chest should be sought in otherwise unexplained arrhythmias and conduction disturbances.

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Stopping smoking and long-term mortality after acute myocardial infarction

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SUMMARY A prospective follow-up study was carried out to investigate the relation between smoking and risk of death after an acute myocardial infarction. The study consisted of male patients under the age of 65 years, who had had an acute myocardial infarction between 1972 and 1975 in North Karelia, Finland. Of these patients, 888 survived the first six months after the acute infarction and were followed-up for three years after the infarction with regard to their deaths. The cumulative all-causes mortality rate of the patients who were still smoking six months after the acute myocardial infarction was 1·7 times that of the patients who had stopped smoking within the first six months. There was a dose-response relation between the number of cigarettes smoked daily and the mortality. The impact of smoking was greatest in the subgroups of patients with an otherwise good prognosis. We estimated that 28 per cent of the deaths in the whole group of initial smokers was attributable to continuing smoking after the infarction. On the basis of these findings we suggest that anti-smoking advice should be an important part of the modern comprehensive care of patients with an acute myocardial infarction.

Some recent investigations show a lower mortality after an acute myocardial infarction in patients who stop smoking than in those who continue.[1–3] There is also evidence that the lower mortality among the ex-smokers is not caused by other factors. In one earlier study the mortality in patients who stopped smoking did not differ from the mortality of those continuing smoking after infarction.[4]

On the basis of the above-mentioned two studies with positive results on the relation between smoking and the prognosis after a myocardial infarction, it has frequently been suggested that anti-smoking measures after a myocardial infarction should be given a high priority when implementing secondary preventive intervention.

The purpose of the present study was to compare the risk of death after acute myocardial infarction in smokers who continued smoking with those who stopped, independent of other factors related to the risk of death, in a representative group of male patients with acute myocardial infarction under the age of 65, and in its risk-specific subgroups.

Subjects and methods

The study consisted of men under the age of 65 who were registered in the community myocardial infarction register of North Karelia in Eastern Finland, which has some 180 000 inhabitants. The registered heart attacks are classified as 'definite' or 'possible' acute myocardial infarction, no infarction, or 'insufficient information' according to the rigid operational criteria that were used in the international co-operative myocardial infarction register study co-ordinated by the WHO.[5 6] The diagnostic criteria and the methods of data collection of the register have been published previously in detail.[7–9] Only patients with a 'definite' or 'possible' acute myocardial infarction, who survived the first six months after the infarction, were included in the study.

Information concerning the deaths and the causes of death of the subjects during the three-year period after the infarction was collected from death certificates.

The data on smoking and medical history before the infarction were gathered in an interview by a nurse as early as possible after the acute phase of the attack. The data connected with the course of the acute period and the diagnostic criteria were collected using a standard questionnaire.

At six months and one year after the infarction, a postal inquiry was made in order to collect information about the health habits (for example, smoking) of the patients.

Received for publication 13 August 1979

The mortality from all causes between six months and three years after infarction of the patients who continued to smoke was compared with that of those who stopped smoking within six months of the infarction. The ratio of mortality of the smokers to that of the non-smokers was used as the statistic measuring the strength of the relation. Its variance and 95 per cent confidence limits were computed using the method concerning ratios of two proportions suggested by Thomas and Gart.[10] The statistical significance of the overall rate ratios was based on the usual χ^2 test of independence in a fourfold table, with Yates' correction for continuity. The results were considered statistically significant when the probability of type I error was less than 0·05. The fraction of mortality attributable to smoking in the whole group was calculated as suggested by Levin.[11] The variance and 95 per cent confidence interval of this statistic were computed as proposed by Walter.[12]

In order to control some of the expected covariates of smoking, we calculated mortality rate ratios after stratifying the material according to the covariates: age, history of previous myocardial infarction and angina pectoris, occurrence of acute heart failure or cardiac arrest, and a combined index of seven variables. The significance of stratum-specific rate ratios was tested using the Fischer exact test, with a doubled value of probability to get a two-tailed significance. When the smallest expected frequency exceeded 10, the χ^2 test with Yates' correction was used. In addition, a summary rate ratio was computed over the strata, in order to control for the confounding effect of some covariates, using the method of direct standardisation with the group of the non-exposed (non-smokers) as the standard as suggested by Miettinen.[13] In computing the summary χ^2 statistics, the Mantel-Haenszel procedure was applied.[14]

Results

There were 888 men registered in the North Karelia myocardial infarction register who passed the criteria for inclusion in the study. At interview after the infarction, 352 men reported not having smoked even one cigarette daily or the equivalent amount of other tobacco in the three months before the infarction; the information on previous smoking was missing in one patient. Two hundred and twenty-one men stopped smoking within six months of the infarction, and 302 men reported in the postal interview that they still smoked six months after the infarction. For 19 patients, the data about smoking six months after infarction was missing. In seven of these, the data concerning the situation at 12 months was used. So there were 12 men (1·3%) with no data on their smoking status at six and 12 months after infarction.

The number of deaths between six months and three years after infarction among the patients giving up and those continuing to smoke is presented in Table 1 according to the cause of death.

Of the initial non-smokers, 52 (14·8 per 100, 95% confidence interval (CI) 11·1 to 18·5) died between six months and three years after the infarction. Among those giving up smoking after the infarction the number of deaths was 26 (11·8 per 100, CI 95% =7·5 to 16·0). Of the patients continuing to smoke after infarction 60 (19·9 per 100, CI 95% =15·4 to 24·4%) died between six months and three years after infarction.

The estimated crude all-causes death rate among the patients continuing to smoke after the infarction was thus 1·7 times that of those who stopped smoking (CI 95% =1·1 to 2·6, $\chi^2=5{\cdot}52$, $p=0{\cdot}019$). The proportion of the deaths attributable to continuing smoking after infarction was 28 per cent (CI 95% =7 to 50%) or 24 (CI 95% =6 to 43)

Table 1 *Deaths between six months and three years after acute myocardial infarction, according to smoking status and cause of death*

Cause of death	*Ex-smokers*	*Current smokers*	*Rate ratio‡*		*Two-tailed significance‖*
			Point estimate	*CI 95%§*	
Ischaemic heart disease*	22	49	1·6	1·0–2·7	0·053
Other cardiovascular disease†	2	4	1·5	0·3–8·0	0·995
Other than cardiovascular disease	2	7	2·6	0·5–12·3	0·379
All deaths	26	60	1·7	1·1–2·6	0·019
Patients at risk	221	302			

* Codes 410–414 according to the International Classification of Diseases (ICD), revision eight.

† ICD codes 390–404 and 420–458.

‡ When calculating the disease category specific mortality rates, the deaths in other diseases are included in the denominator.

§ See text.

‖ See text.

Table 2 *Deaths from all causes between six months and three years after acute myocardial infarction, according to number of cigarettes smoked daily six months after infarction*

	Ex-smokers	*Current smokers*			
		1–4	*5–14*	*≥15*	*All smokers*
Deaths	26	9	33	18	60
Patients at risk	221	60	164	78	302
Mortality rate (%)	11·8	15·0	20·1	23·1	19·9
CI 95%*	7·5–16·0	6·0–24·0	14·0–26·3	13·7–32·4	15·4–24·4
Rate ratio†		1·3	1·7	2·0	1·7
CI 95%‡		0·6–2·2	1·1–2·7	1·1–3·0	1·1–2·6

* Calculated based on the assumption of binomial distribution.
† Smokers in specific category of number of cigarettes smoked versus ex-smokers.
‡ See text.

out of the 86 deaths in the whole group.

When only the deaths between six and 12 months after the infarction are considered, the all-causes mortality rate ratio between smokers six months after the infarction and ex-smokers was 2·4 (CI 95% =1·0 to 6·0, χ^2=4·06, p=0·044). The respective rate ratio for deaths between six months and two years after the infarction was 2·0 (CI 95%=1·2 to 3·4, χ^2=6·12, p=0·013).

In the subgroup of patients with a 'definite' acute myocardial infarction the ratio of death rates between six months and three years comparing current smokers and ex-smokers was 1·7 (CI 95%= 1·1 to 2·7, χ^2=4·73, p=0·030).

In the whole group, 82·6 per cent of all deaths were the result of ischaemic heart disease. The smoking-related ischaemic heart disease mortality rate ratio of smokers to ex-smokers did not reach statistical significance ($p > 0{\cdot}05$) and did not differ significantly from the respective all-causes mortality rate ratio. The relative mortality for all cardiovascular diseases was 1·6 (CI 95%=1·0 to 2·6), and showed significance according to the test statistic (χ^2=4·03, p=0·045) (Table 1). In order to study the existence of a dose-response relation between smoking and mortality after acute myocardial infarction, we examined the cumulative all-causes mortality from six months to three years after infarction at different levels of smoking (Table 2).

There was a trend for the rate ratio to increase with the number of cigarettes smoked daily.

In order to control the possible confounding effect of some factors expected to affect the mortality after acute myocardial infarction, all subjects were categorised first by age (Table 3) and, secondly, by history of previous acute myocardial infarction and/or angina pectoris and occurrence of acute cardiac failure and/or cardiac arrest during the acute phase (Table 4).

While the total mortality after acute myocardial infarction increased slightly with age, the death ratio related to smoking after infarction did not show any consistent trend by age. There was no significant difference in the age distributions of ex-smokers and current smokers. For this reason no age adjustment is included in the analysis of the

Table 3 *Deaths from all causes between six months and three years after acute myocardial infarction, according to smoking status and age at onset of attack*

Age (y)		*Ex-smokers*	*Current smokers*	*Rate ratio*		*Two-tailed significance*
				Point estimate	*CI 95%*	
28–44	Deaths	4	13			
	Patients at risk	37	61	2·0	0·7–5·9	0·290
45–54	Deaths	9	22			
	Patients at risk	94	111	2·1	1·0–4·4	0·062
55–64	Deaths	13	25			
	Patients at risk	90	130	1·3	0·7–2·5	0·458
	Crude total					
	Deaths	26	60			
	Patients at risk	221	302	1·7	1·1–2·6	0·019
	Adjusted summary*			1·7		0·014

* Computed using five-year age categories.

Table 4 *Deaths from all causes between six months and three years after acute myocardial infarction according to smoking status six months after infarction, history of previous infarction or angina pectoris, and occurrence of acute heart failure or cardiac arrest within first month after infarction*

	Ex-smokers		*Current smokers*		*Rate ratio*		*Two-tailed significance*
	Deaths	*Patients at risk*	*Deaths*	*Patients at risk*	*Point estimate*	*CI 95%*	
No history of AMI or AP							
No AHF or CA	4	57	13	77	2·4	0·8–7·2	0·147
ACF or CA	2	21	3	18	1·8	0·3–9·9	0·848
Previous AMI or AP							
No AHF or CA	9	101	26	147	2·0	1·0–4·2	0·073
AHF or CA	11	42	18	60	1·1	0·5–2·3	0·835
Crude total	26	221	60	302	1·7	1·1–2·6	0·019
Adjusted summary					1·7		0·014

AMI, acute myocardial infarction; AP, angina pectoris; AHF, acute heart failure; CA, cardiac arrest.

importance of other possible confounding factors.

The smoking-related death rate ratio was insignificantly higher in the 'low-risk' subgroups, that is, in patients who had no other factors likely to contribute to high risk of death. Among patients without previous acute myocardial infarction or angina pectoris and without acute heart failure or cardiac arrest in the acute phase, the estimate of the rate ratio was 2·4 but did not deviate significantly from unity (Table 4). Previous acute myocardial infarction or angina pectoris was more prevalent among smokers than among non-smokers (69% vs 65%). The smoking-related mortality rate ratio was also calculated according to the number of some selected factors contributing to mortality. These factors were age, diagnostic category of infarction, history of previous acute myocardial infarction, prodromal or previous angina pectoris, acute heart failure at the onset of attack, or during the hospital treatment, and cardiac arrest during the the hospital treatment (Table 5).

There was a slight downward trend in the smoking-related rate ratio with increasing number of other post-myocardial infarction risk factors (Table 5). The mortality of the smokers with not more than one of these risk factors was almost five times higher than that of the patients who stopped smoking. There were more smokers than ex-smokers having at least four of the risk factors (18% vs 11%). The adjusted summary rate ratio calculated over the four strata was 1·6 and still statistically significant (Mantel-Haenszel χ^2 with 1 df=3·93, p=0·035).

Discussion

The purpose of the study was to investigate the relation between stopping smoking and long-term mortality after acute myocardial infarction, considering simultaneously some of the other factors contributing to this mortality and examining this relation in subgroups of patients with different risks of death.

For the study we chose all male patients under the age of 65, who had suffered a definite or a possible acute myocardial infarction according to

Table 5 *Deaths from all causes between six months and three years after acute myocardial infarction according to smoking status and number of selected factors related to risk of death*

*Number of risk factors**	*Ex-smokers*		*Current smokers*		*Rate ratio*		*Two-tailed significance*
	Deaths	*Patients at risk*	*Deaths*	*Patients at risk*	*Point estimate*	*CI 95%*	
0–1	2	57	11	64	4·9	1·2–21·9	0·028
2	6	70	20	108	2·1	0·9–5·2	0·108
3	9	70	13	77	1·3	0·5–2·9	0·649
4–7	9	24	16	53	0·8	0·3–1·7	0·710
Crude total	26	221	60	302	1·7	1·1–2·6	0·019
Adjusted summary					1·6		0·035

* The value of an additive index consisting of items age (28–54=0, 55–64=1); diagnostic category of infarction (possible=0, definite=1); history of previous acute myocardial infarction (no=0, yes=1); prodromal or previous angina pectoris (not either=0, one or both=1); acute heart failure at onset of attack (no=0, yes=1); acute heart failure during hospital treatment (no=0, yes=1); cardiac arrest during hospital treatment (no=0, yes=1).

the North Karelia community myocardial infarction register, and who had survived the first six months after the onset of symptoms.

The patients were from a complete unselected four-year series of men under 65 years of age with myocardial infarction who were detected in a geographically and administratively defined population. The diagnostic validity of the registration has been considered earlier, based on a blind reclassification into the defined diagnostic categories of a sample of the registered heart attacks.[9] The coverage of the registration is being cross-checked against the national hospital discharge data.

The patients dying within the first six months after the infarction were not included in the study because the data concerning change in smoking habit were not available earlier than six months after the infarction. This resulted in a reduction of the study population but also decreased the possible confounding effect of infarct size and severity of infarction on the relation between smoking and mortality.

The data on smoking were almost complete though reliance had to be placed on a mailed questionnaire. The relation of smoking to mortality was studied solely on the basis of the deaths occurring after the measurement of smoking, and the smoking status during the follow-up of 'outcome events' (deaths) was not taken into account in the analysis, so that any bias caused by the selective missing data concerning smoking because of deaths could be avoided. It also follows, however, from the design that there might have been some 'drop-out' and 'drop-in' of smokers into the 'reference group', that is, ex-smokers and vice versa. It is likely that some smokers stopped smoking six months after the infarction, and some of those who had stopped smoking before six months started again afterwards. This assumption is supported by the finding that the mortality ratio between smokers and ex-smokers was higher when shorter periods of follow-up were considered. The contamination between the exposed and the non-exposed—the random error in the measurement of exposure—would have caused underestimation of the rate ratios.

The ratio of the mortality rate of smokers to that of ex-smokers was used as an estimator of relative risk, a measurement of the strength of the relation between smoking and survival. This was possible because of the prospective nature of the study. The use of the odds ratio (cross-product ratio) as an estimator of relative risk was considered improper because of the relatively high rate of outcome events, which exceeded the limit of 10 per cent that has been suggested as the maximum to make the approximation possible.[15] The use of the odds ratio, as has been done in some studies with a similar design would probably have resulted in an overestimation of relative risks. In addition, the measure of statistical significance, χ^2 with the correction for continuity, is a conservative test statistic and leads to two-sided testing of the relation studied.

It is possible that the design of the study and the statistical analysis of the data produce a bias towards accepting the null hypothesis rather than rejecting it. If smoking status after infarction had been defined in another way, its relation to mortality after infarction would probably have seemed closer.

Summary χ^2 statistics were used as presented by Mantel and Haenszel,[14] in which the weights for the strata of the covariate are given partly on the basis of their relative importance and partly to minimise the variance. According to the authors, the use of this summary statistic does not require the assumption of homogeneity of rate ratio over the strata to be combined. The use of the Mantel-Haenszel rate ratio statistic has been recommended as a combined estimator of the odds ratio, when the number of strata is more than two.[16]

In the whole group of initial smokers the total mortality between six months and three years after the infarction was 1·7 times and respective mortality from ischaemic heart disease was 1·6 times higher in the patients who continued to smoke than in those who gave up smoking within six months of infarction. The total mortality rate ratio was exactly the same in patients registered as having a definite acute myocardial infarction according to the defined rigid operational criteria.

It was found that the all-causes mortality in those giving up smoking was somewhat lower than that in initial non-smokers. This could be explained in two ways. Firstly, it is likely that initial smokers had a higher early mortality than non-smokers, as suggested by some previous studies.[8 17] Therefore there might have been more patients with a severe course of infarction in the acute period who remained among the initial non-smokers. Secondly, those who did not smoke before the infarction must, on average, have had some factors other than smoking which increased the risk of infarction and probably also later the risk of death.

The strength of the relation between smoking and risk of death after acute myocardial infarction seemed to be increased in the subgroups of patients with a lower risk according to other factors contributing to post-myocardial infarction mortality. According to these data, the impact of smoking after acute myocardial infarction is almost twice as great among patients without a previous infarction or angina pectoris, and more than two-thirds greater among those without acute heart failure or cardiac arrest during the acute period of infarction, as compared with the others. The results of the analysis where seven important predictors of death after infarction were taken into account, also support the finding that continuing smoking after acute myocardial infarction is related to the greatest extra risk of death in the patients who otherwise would have had a good prognosis in terms of survival.

Among 405 male patients with a first myocardial infarction, aged 67 and below, who were registered in the Gothenburg myocardial infarction register, the patients who continued to smoke had a 1·9 times greater all-causes two-year mortality after infarction than those who had stopped smoking within three months of the infarction.[1] In the series of 190 patients with a first attack of acute coronary insufficiency or myocardial infarction, aged under 60, who were admitted to the cardiac department at St. Vincent's Hospital, Dublin, and who had survived 28 days or longer, the respective cumulative five-year mortality rate ratio was 1·6. The mortality of the patients who did not reduce their smoking (or did so by less than 50%) was twice as high as those who stopped or reduced smoking by at least 50 per cent (calculated on the basis of the figures given in Table 3[3]). The strength of the relation in these two previous studies is of the same magnitude as that observed in the present study.

In the latter study, the relation of smoking to mortality after the infarction was also considered separately in the group of patients with acute coronary insufficiency or an 'uncomplicated' myocardial infarction and with a 'complicated' myocardial infarction. The rate ratios in these two subgroups between smokers and those who stopped or reduced were 1·4 and 4·0 (Table 4).[3] Though not significant, this finding is not in agreement with the present study finding that smoking might have its greatest importance among patients with acute myocardial infarction without 'complications'. The lack of agreement could be caused by the small number of deaths in the Irish study, resulting in a large sampling variation, and by the difference in the selection of 'complications' that were taken into consideration.

In the present study there was a direct, statistically significant overall association between smoking and long-term prognosis after an acute myocardial infarction and a clear dose-response relation. In addition, the measurement of smoking preceded the observation of mortality, and the association remained significant, when the effect of some of the most important confounding factors was removed. So, assuming that there were no other extraneous factors producing a pseudoassociation, the association could be considered as a causal one, the mechanisms of which remain to be explained.

Because of the representativeness of the material the results seem to be applicable to any infarction patient population with similar characteristics. The existence of a common causal relation is supported by earlier similar findings. It is probable that the relation is strongest among patients with an otherwise good prognosis.

On the basis of our findings we estimated that among patients who had smoked before the infarction, 28 per cent, or 24 out of the 86 deaths, were attributable to continuing to smoke after the infarction and thus could, theoretically, have been prevented for three years at least by complete control of smoking after the infarction. For the reason that smoking seems to be one of the few things affecting the prognosis after an acute myocardial infarction which can be modified permanently and without any side effects, anti-smoking advice should be an essential part of the modern comprehensive care of these patients.

Our findings suggest that an individual patient who had smoked before the infarction could reduce his risk of dying during the next years by one-third by giving up smoking after the infarction. This information could be useful in motivating the patients with an acute myocardial infarction to stop smoking.

Because of the considerable prognostic impact of smoking, further studies on the methods of anti-smoking health education among the patients with an acute myocardial infarction are needed.

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Br Heart J 1980; **43:** 470–3

Left vocal cord paralysis and dysphagia in mitral valve disease

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SUMMARY Two cases of severe mitral stenosis with both hoarseness, caused by left vocal cord palsy, and dysphagia are described. This combination in the same patient has not, to our knowledge, been previously described.

Previous studies have firmly established that vocal cord paralysis in mitral stenosis is a result of compression of the left recurrent laryngeal nerve as it passes around the aortic arch. It is suggested that dysphagia may also develop as a result of neurological damage, in this case to autonomic nerve plexuses supplying the oesophagus, leading to abnormal peristalsis and enabling external compression by a tense left atrium sufficient to cause symptoms.

Left vocal cord paralysis and dysphagia are uncommon complications of mitral valve disease. Since first described by Ortner,[1] studies have indicated that left recurrent nerve palsy occurs in less than 1 per cent of patients with mitral stenosis.[2] Dysphagia has been reported in only a small number of patients.[3–6]

After an extensive search of the world's publications we have been unable to find any reported cases of mitral stenosis with both hoarseness, caused by left recurrent laryngeal nerve palsy, and dysphagia. We report two such patients and discuss the mechanisms by which the abnormalities may arise.

Received for publication 27 July 1979

Case 1

This patient developed palpitation at the age of 55, when she was found to have mitral stenosis with atrial fibrillation; there was no history of rheumatic fever. The palpitation settled with digoxin, and she

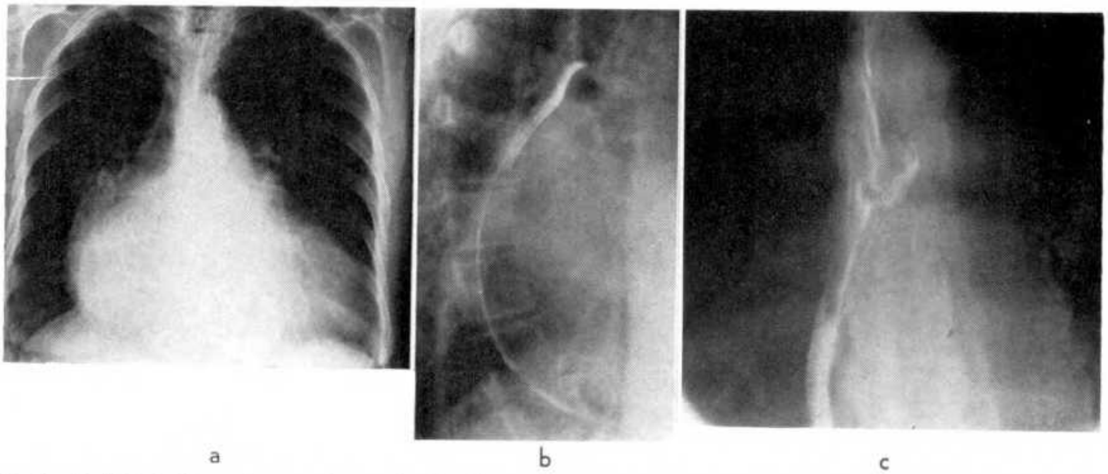

Fig. 1 *Radiological investigations in case 1.* (a) *Chest* X-*ray, showing conspicuous cardiomegaly with gross left atrial enlargement.* (b) *Barium swallow (right anterior oblique projection) showing backward displacement of the oesophagus around the enlarged left atrium.* (c) *Hilar tomography during the barium swallow showing delayed passage of contrast material at the angle of tracheal bifurcation and pronounced upward displacement of the left main bronchus.*

remained well for 10 years when mild effort dyspnoea developed. Five years later she became hoarse, and subsequent laryngoscopy revealed complete paralysis of the left vocal cord. Over the next two years she noticed difficulty in swallowing solid foods, which felt to her as if they were sticking in the middle of her chest. She had also become more breathless with effort and slept with four pillows to avoid orthopnoea.

On examination, she was in atrial fibrillation with a slight increase in jugular venous pressure, right ventricular enlargement, and the auscultatory findings of severe mitral stenosis. The electrocardiogram was compatible with these findings. Her chest *x*-ray film showed distinct cardiomegaly (Fig. 1a). At cardiac catheterisation the indirect left atrial pressure was 30 mmHg (mean) and she was found to have an end-diastolic gradient across the mitral valve of 15 mmHg and a pulmonary artery pressure of 90/40 mmHg. Left ventricular angiography showed trivial mitral reflux. Finally, barium studies showed considerable backward displacement of the oesophagus with delayed passage of dye through the mid-portion (Fig. 1b), and hilar tomography during the barium examination indicated gross widening of the angle of tracheal bifurcation (Fig. 1c).

A diagnosis of severe mitral stenosis with pulmonary hypertension was made. She declined operation and is being treated with digoxin and diuretics.

Case 2

At the age of 41 this housewife underwent mitral valvotomy because of increasing breathlessness secondary to mitral stenosis. There was no history of rheumatic fever. Ten years later she sustained a left hemiplegia from which she made a complete recovery. She was virtually asymptomatic for a further three years, when effort dyspnoea and ankle oedema developed, and two years later she was admitted to hospital in acute pulmonary oedema which improved with diuretic treatment. She underwent cardiac catheterisation when severe mitral stenosis with a gradient of 15 mmHg was found. Pulmonary artery pressure was 55/20 mmHg, with mean indirect left atrial pressure of 20 mmHg ('v' wave, 30 mmHg). Angiography disclosed trivial

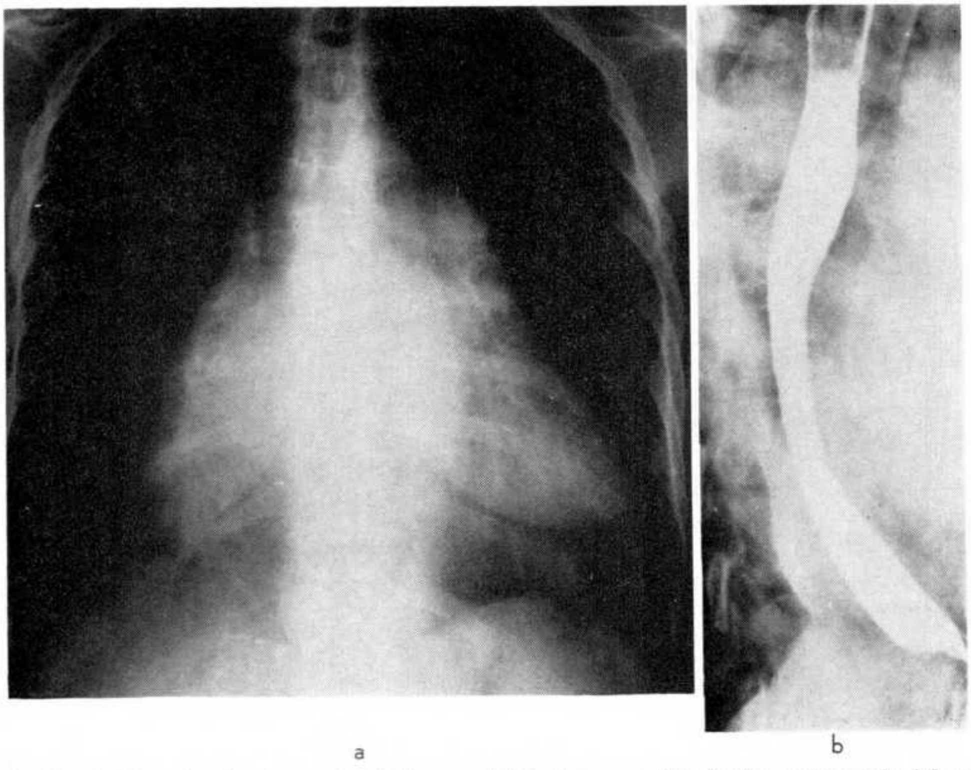

Fig. 2 *Radiological investigations in case 2.* (a) *Penetrated PA chest x-ray film showing cardiomegaly, left atrial enlargement, prominent left pulmonary artery, and upward displacement of the left main bronchus.* (b) *Barium swallow (right anterior oblique projection) showing compression and backward displacement of the oesophagus.*

mitral regurgitation and slight aortic regurgitation; left ventricular contraction was normal. She declined operation but subsequently became increasingly breathless with effort and developed both dysphagia and hoarseness. At laryngoscopy the left vocal cord was noted to be completely paralysed.

She was readmitted to hospital. The venous pressure was slightly raised and both ventricles were clinically enlarged. Auscultatory findings were of severe mitral stenosis and slight aortic regurgitation. The electrocardiogram showed right axis deviation with digoxin effect and her chest x-ray film showed severe cardiomegaly with left atrial enlargement and upward displacement of the left main bronchus (Fig. 2a). At barium swallow oesophageal displacement and compression were shown (Fig. 2b).

She underwent mitral valve replacement surgery with a Björk-Shiley prosthesis and her postoperative progress was uneventful, though she was still hoarse when examined six weeks later. She died suddenly two months after operation but there was no necropsy.

Discussion

Left vocal cord paralysis in mitral stenosis is caused by compression of the left recurrent laryngeal nerve between the aortic arch and the pulmonary artery[7] which is displaced upwards by the enlarged left atrium (Fig. 3a). Enlarged tracheobronchial lymph nodes may be an additional contributory factor.[8] The mechanisms of dysphagia in association with mitral valve disease are less certain. Normal swallowing is controlled and co-ordinated by autonomic nerve plexuses in the oesophagus. These plexuses derive their nerve supply from the vagus nerves and thoracic sympathetic outflow; fibres form the posterior pulmonary plexuses from which four or five cords pass posteriorly to the middle of the oesophagus. The cords then divide into the oesophageal plexus which supplies afferent and efferent fibres (Fig. 3b). During normal peristaltic contraction, pressure within the oesophageal lumen reaches peak values of 40 to 80 mmHg.[9]

In severe mitral stenosis the enlarged left atrium displaces the oesophagus, usually backwards and to the right.[5] [6] Pressure within the left atrium is increased and may interfere with normal oesophageal peristalsis sufficient to cause dysphagia, though the maximum pressure applied to the oesophagus by the left atrium is never likely to exceed peak intra-oesophageal pressure during active peristalsis. However, autonomic nerve fibres stretched between the posterior pulmonary plexuses and the oesophagus may themselves be damaged, resulting in abnormal oesophageal peristalsis and

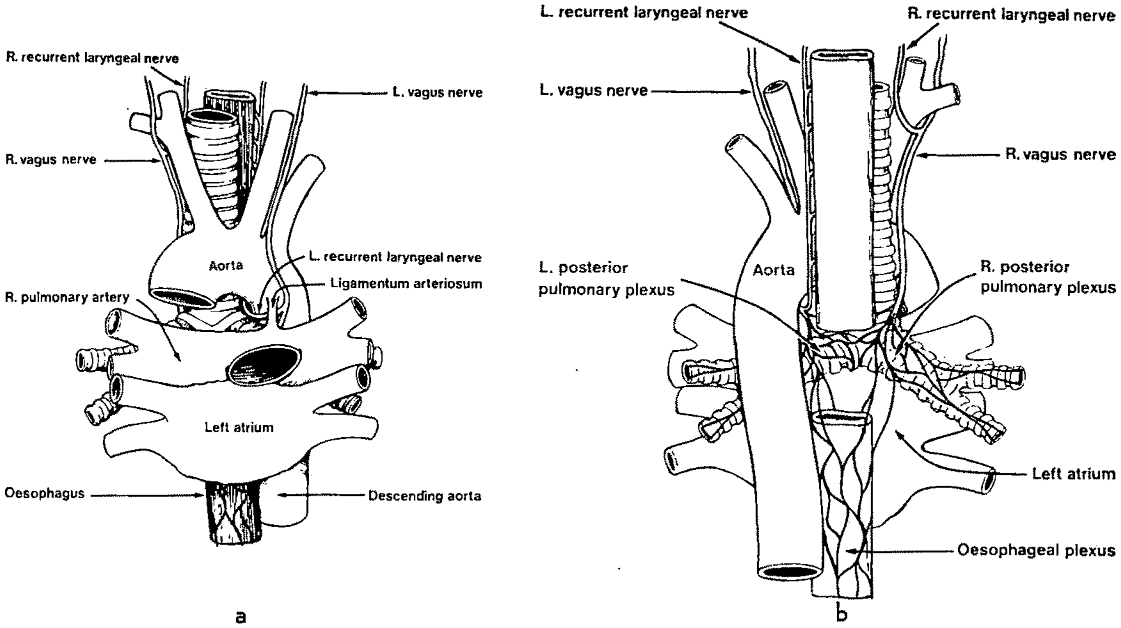

Fig. 3 *Normal anatomical relations of the left atrium (drawn by J Abbott).* (a) *Anterior view showing the left recurrent laryngeal nerve passing around the aortic arch, behind the ligamentum arteriosum and above the left pulmonary artery and left main bronchus.* (b) *Posterior view showing division of the vagus nerves into posterior pulmonary plexi, from which fibres pass over the left atrium to the oesophagus.*

an increased likelihood to dysphagia developing as a result of external compression from the enlarged and tense left atrium.

The two patients described in this paper developed both hoarseness and dysphagia as the severity of the mitral valve disease increased. In each case hoarseness was found at laryngoscopy to be caused by left vocal cord paralysis. Dysphagia was not sufficient to cause extreme difficulty in swallowing in either patient though both described the sensation of food sticking at mid-thorax level. Barium swallow showed conspicuous oesophageal displacement around an enlarged left atrium in each patient, and there is no doubt that the degree of displacement would have been sufficient to stretch, and possibly damage, nerves supplying the oesophageal plexus.

We thank Dr W Brigden for permission to report these cases under his care and for his help in the preparation of this paper.

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Br Heart J 1980; **43:** 474–80

Right and left ventricular performance in ambulatory young adults with cystic fibrosis*

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SUMMARY Although cystic fibrosis is noted primarily for pronounced abnormalities in pulmonary function, a substantial number of patients die as a result of cardiac complications. Nevertheless, little is known about cardiac performance in this disease. The cardiac pathophysiological consequences of cystic fibrosis were investigated non-invasively by measuring right and left ventricular performance using radionuclide angiocardiography. Studies were performed in 22 ambulatory young adults with cystic fibrosis and clinically evident pulmonary disease. Right ventricular ejection fraction was abnormal ($<45\%$) in nine patients, while left ventricular ejection fraction was normal ($\geqslant 55\%$) in all 22 patients. Within one year of radionuclide evaluation, four patients with depressed baseline right ventricular function developed acute cor pulmonale and died. The presence of abnormal right ventricular performance was related to the severity of cystic fibrosis. Arterial oxygen tension, forced expiratory volume in one second, and forced vital capacity were significantly less in patients with abnormal right ventricular ejection fraction than in those with normal function. All six patients with severe disease (Schwachman clinical score $\leqslant 40$) had abnormal right ventricular ejection fraction, while none of 10 with good to excellent scores had abnormal right ventricular function. Radionuclide angiocardiography allows non-invasive detection of right ventricular dysfunction at a time when it would not be appreciated by conventional clinical methods. This approach provides pathophysiological insights into the haemodynamic abnormalities associated with this disease and may also allow the response to treatment to be monitored.

Cor pulmonale and respiratory failure are common in cystic fibrosis, particularly at the time of death.[1–8] Unfortunately, right ventricular hypertrophy and right heart failure frequently are difficult to identify before overt cardiopulmonary decompensation.[5 6 9–11] Because of a lack of accurate non-invasive techniques, the relation between the severity of cystic fibrosis and right and left ventricular performance has not been determined. In fact, relatively little is known about the early pathophysiological abnormalities in cardiac performance which commonly are undetected before the development of cor pulmonale.

Non-invasive techniques suitable for the study of cardiac performance are needed for assessment of functional status in patients with cystic fibrosis. Echocardiography previously has been used to measure right ventricular wall thickness and cavity dimensions.[9–11] However, this technique is limited theoretically by geometric assumptions not necessarily appropriate for the right ventricle and technically by difficulties encountered in studying patients with thoracic hyperinflation caused by lung disease. Quantitative radionuclide angiocardiography is an alternative non-invasive method which allows evaluation of both right and left ventricular ejection fractions from regional radionuclide time-activity curves. This technique is free of assumptions concerning the geometric configurations of the two ventricles and technically is unaffected by the presence of concomitant lung

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*Supported in part by a National Heart, Lung and Blood Institute grant, Bethesda, Maryland, USA.

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Received for publication 3 May 1979.

disease. A previous study from this laboratory has shown that this radionuclide technique allows detection of right ventricular dysfunction before development of clinically evident cor pulmonale in patients with chronic bronchitis and emphysema.[12] In addition, intravenous aminophylline has been found to improve biventricular performance determined by this technique in the same patient population.[13] This radionuclide method has also been used to evaluate a broad spectrum of patients with coronary and congenital heart disease.[14–18] The present report describes the application of quantitative radionuclide angiocardiography to the assessment of right and left heart performance in cystic fibrosis.

Patients and methods

PATIENT SELECTION

Twenty-two young adults (13 male and nine female) with cystic fibrosis were included in this study. The mean age was 20 years (range 14 to 27 years) and all had clinically apparent pulmonary disease. The diagnosis was established from conventional clinical findings and sweat electrolyte tests.[2] The severity of cystic fibrosis was assessed, without knowledge of cardiac or pulmonary function data, by one investigator (TD) using the Schwachman clinical scoring system.[2] Briefly, this system assigns a maximum of 25 points to each of four categories: general activity, physical examination, nutrition, and chest radiograph. The grading system is divided as follows: severe (⩽40 points), mild to moderate (41 to 70 points), and good to excellent (71 to 100 points). According to these criteria, six patients were severe, six were mild to moderate, and 10 were good to excellent. All patients were ambulatory and fully compensated without evidence of right or left heart failure.

At the time of entry into the study, a radionuclide angiocardiogram, pulmonary function tests, arterial blood gases, and a 12 lead electrocardiogram were obtained. Three patients (cases 7, 10, and 16) refused arterial blood gas tests. All patients were followed clinically for at least two years or until death. Informed consent was obtained from each patient or, if necessary, from a parent, according to procedures established by the Human Investigation Commiittee of Yale University School of Medicine.

RADIONUCLIDE TECHNIQUE

Patients were studied supine in the anterior position using a computerised multicrystal scintillation camera (Cordis-Baird System-77, Bedford, Massachusetts). Twenty mCi technetium-99m pertechnetate were injected in the right antecubital vein. The initial transit of radioactivity through the central circulation was recorded at 20 frames/second for approximately 25 seconds. Right ventricular and left ventricular ejection fractions were determined in a standardised and reproducible manner from quantitative radionuclide angiocardiograms using techniques developed and validated in this laboratory.[12 14] Individual ejection fractions from each ventricle are obtained readily with this technique, since there is anatomical and temporal separation of the radionuclide bolus as it traverses the central circulation. The multicrystal camera as present commercially available allows accumulation of high count rate data (up to 450 000 counts/s) without dead-time losses, such that statistical uncertainty is minimised. In 50 normal subjects without cardiopulmonary disease, right ventricular ejection fraction was 55±5 per cent (mean ±1 SD).[12] The normal range, expressed as the mean ±2 standard deviations, was 45 to 65 per cent. Normal left ventricular ejection fraction is 55 per cent or more.

PULMONARY FUNCTION TESTS AND ARTERIAL BLOOD GASES

Forced expiratory volume in one second and forced vital capacity were measured using a computerised flow-volume system.[19] Data were also expressed as a percentage of predicted value based upon age and sex.[20] Arterial blood gases were obtained while patients were breathing room air.

STATISTICAL DATA

Data are expressed as the mean ± standard error. Comparisons between two groups were made by Student's t test and between three groups by analysis of the variance (F test) using conventional techniques.[21]

Results

Right ventricular ejection fraction was abnormal (<45%) in nine patients (range 39 to 44%) and normal in the remaining 13 patients (range 49 to 64%) (Table, and Fig. 1). Left ventricular ejection fraction was normal in all 22 patients, with a range of 56 to 80 per cent. During the first year of follow-up, four patients (cases 1, 2, 4, and 6) developed cor pulmonale with acute respiratory failure[22] and right-sided heart failure. One additional patient (case 7) developed acute respiratory failure without right-sided heart failure. Right ventricular ejection fraction determined six to 12 months (mean eight months) before clinical decompensation was moderately abnormal in all five cases (range 39 to

44%). All four patients with cor pulmonale subsequently died as a result of cardiorespiratory failure. Necropsy data were available in two patients (cases 1 and 4), and both had evidence of right ventricular hypertrophy and dilatation.[6] [23] The left ventricle was normal in both cases. No other patient in the study died within the follow-up period. Of the 22 patients in the study, only two patients (cases 4 and 6) had electrocardiographic evidence of right ventricular hypertrophy[24] (right ventricular ejection fractions, 39 and 41%). At the time of data analysis, four patients (cases 3, 4, 9, and 11) have radionuclide evidence of right ventricular dysfunction but are clinically stable. None of these four patients or the 13 with normal right ventricular ejection fraction have signs or symptoms of cor pulmonale.

The presence of right ventricular dysfunction was related to the severity of cystic fibrosis as determined by the Schwachman clinical score. Right ventricular ejection fraction was 42 ± 1 per cent (mean $\pm$ SEM) in patients with severe cystic fibrosis, compared with 49 ± 3 per cent in those with mild to moderate clinical scores, and 56 ± 2 per cent in those with good to excellent scores ($p < 0\cdot001$ for between group means) (Fig. 2). All six patients with severe disease had abnormal right ventricular ejection fraction (range 39 to 44%), while none of 10 with good to excellent scores had abnormal right ventricular function (range 49 to 64%). In addition, three of six with mild to moderate cystic fibrosis also had abnormal right ventricular function. When approached in an alternative way, patients with abnormal right ventricular ejection fraction had a Schwachman score of 42 ± 4 points, which was significantly less than in those with normal right ventricular function (73 ± 3 points, $p < 0\cdot001$).

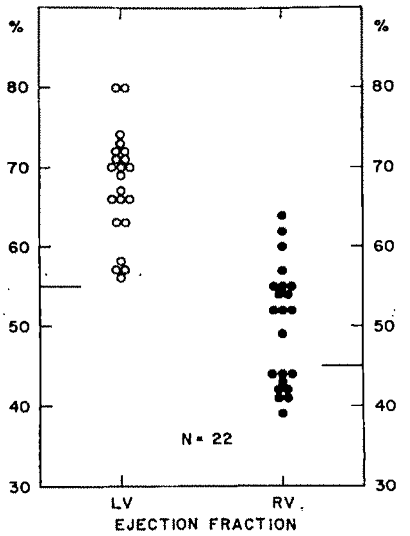

Fig. 1 *Left ventricular (LV) and right ventricular (RV) ejection fraction in 22 patients with cystic fibrosis. RV ejection fraction is abnormal (<45%) in nine, while LV ejection fraction is abnormal (<55%) in none. N, number of patients.*

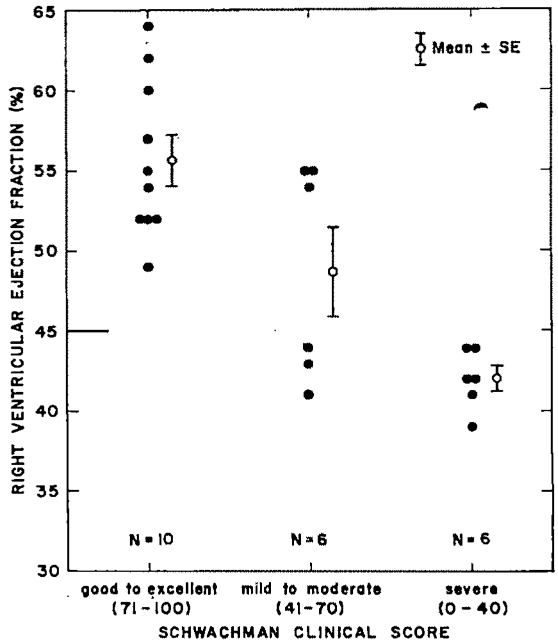

Fig. 2 *Right ventricular ejection fraction compared with Schwachman clinical score in 22 patients with cystic fibrosis. Right ventricular ejection fraction is abnormal (<45%) in all six patients with a Schwachman score ≤40, in three of six with a score of 41 to 70, and in none of 10 with a score of >70. The differences between groups were significantly greater than within groups ($p < 0\cdot001$). N, number of patients; SE, standard error of the mean.*

Arterial oxygen tension was significantly less in patients with abnormal right ventricular ejection fraction than in those with normal function (45 ± 2 vs. 73 ± 3 mmHg, $p < 0\cdot001$) (Fig. 3). All eight patients with severe arterial hypoxaemia (oxygen tension ≤50 mmHg) had abnormal right ventricular ejection fraction (range 39 to 44%). Similarly, arterial carbon dioxide tension was significantly greater in patients with abnormal right ventricular ejection fraction than in those with normal function (46 ± 4 vs. 35 ± 1 mmHg, $p < 0\cdot01$). All five patients with hypercapnia (carbon dioxide tension ≥45 mmHg) had abnormal right ventricular ejection fraction (range 39 to 44%) (Table).

Forced expiratory volume in one second was 32±5 per cent of predicted in patients with abnormal right ventricular performance, compared with 68±6 per cent of predicted in those with normal ejection fraction ($p<0{\cdot}01$) (Fig. 4). Seven of nine patients with abnormal right ventricular ejection fraction demonstrated a forced expiratory volume in one second less than 35 per cent of predicted and less than 1 litre, indicative of pronounced obstructive ventilatory impairment (Table). Forced vital capacity was 46±7 per cent of predicted in patients with depressed right ventricular function, compared with 84±6 per cent of predicted in those with normal ejection fraction ($p<0{\cdot}001$).

Discussion

This non-invasive study has evaluated right and left heart performance in cystic fibrosis and defined the pathophysiological relation between compromise in right ventricular performance and disease severity. Right ventricular dysfunction was present in nine of 22 ambulatory young adults with cystic fibrosis and clinical evidence of pulmonary disease. An abnormal right ventricular ejection fraction was noted in all six with severe disease, in three of six with mild to moderate disease, and in none of 10 with good to excellent Schwachman score. Presence

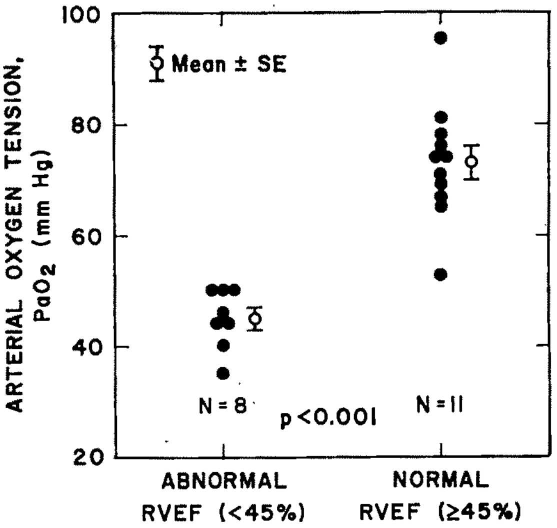

Fig. 3 *Arterial oxygen tension in 19 patients with cystic fibrosis. Arterial oxygen tension is significantly lower in patients with an abnormal right ventricular ejection fraction (RVEF) than in those with a normal right ventricular ejection fraction. Arterial oxygen tension is ≤50 mmHg in all patients with an abnormal right ventricular ejection fraction and in none with a normal right ventricular ejection fraction. N, number of patients; SE, standard error of the mean; p, probability.*

Table *Clinical characteristics, pulmonary function data, and radionuclide ventricular performance data*

Case no.	*Age (y) and sex*	*Schwachman clinical score*	*Arterial blood gases*			*Pulmonary function tests*					*Radionuclide data*	
			pH	P_{CO_2}	P_{O_2}	*FEV₁ (litres)*	*FEV₁ (% pred.)*	*FVC (litres)*	*FVC (% pred.)*	*FEV₁/FVC (%)*	*LVEF (%)*	*RVEF (%)*
1	22 F	25	7·35	56	50	0·93	30	1·83	52	51	69	44
2	21 F	33	7·46	56	40	0·65	24	0·98	32	66	67	44
3	18 M	36	7·47	39	50	0·80	20	0·88	20	91	66	42
4	25 M	37	7·38	57	35	0·50	13	1·45	33	35	80	39
5	21 F	40	7·40	47	50	0·75	24	1·98	56	38	63	42
6	23 F	40	7·40	54	44	0·66	23	0·91	27	73	72	41
7	17 M	44	—	—	—	0·90	32	1·29	42	70	71	41
8	23 F	49	7·41	40	53	0·78	27	1·63	49	48	63	55
9	18 M	57	7·46	36	46	2·65	59	3·49	67	76	74	43
10	17 M	65	—	—	—	1·50	43	2·15	54	70	56	55
11	17 M	65	7·46	24	44	2·50	59	4·00	81	63	70	44
12	21 M	68	7·46	30	71	3·33	74	4·53	86	74	72	54
13	14 F	71	7·45	32	74	1·05	51	1·54	71	68	70	52
14	15 F	72	7·43	35	78	2·20	75	3·09	97	71	70	64
15	17 M	72	7·46	37	76	2·35	69	3·35	91	70	63	54
16	19 M	76	—	—	—	2·95	67	4·50	87	66	80	52
17	25 F	77	7·46	30	63	1·68	54	2·25	62	75	71	60
18	27 F	78	7·44	34	67	1·96	63	3·10	86	63	73	57
19	17 M	79	7·49	35	76	4·16	92	4·83	92	86	66	52
20	15 M	79	7·41	43	81	2·96	89	3·80	100	78	57	55
21	20 M	83	7·49	35	69	3·16	73	4·52	91	70	66	62
22	20 M	86	7·44	30	95	4·84	112	6·40	128	76	57	49

Definitions of abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction (normal ≥ 55%); P_{CO_2}, arterial carbon dioxide tension, mmHg; P_{O_2}, arterial oxygen tension, mmHg; pred., predicted; RVEF, right ventricular ejection fraction (normal ≥ 45%); Schwachman clinical score: severe (0 to 40), mild to moderate (41 to 70), good to excellent (71 to 100).

of abnormal right ventricular performance was related to the severity of cystic fibrosis as assessed by Schwachman clinical score, the presence of arterial hypoxaemia and hypercapnia, and the degree of ventilatory impairment. These data suggest that in cystic fibrosis normal resting right ventricular performance is maintained in most cases until clinically severe disease is present. The abnormalities in right ventricular performance generally were not severe at the time of preclinical detection and were more modest than those noted in adult patients with long-standing chonic bronchitis.[12]

Most patients with an abnormal right ventricular ejection fraction will have a Schwachman clinical score ⩽40 points (severe disease), arterial oxygen tension ⩽50 mmHg, arterial carbon dioxide tension ⩾45 mmHg, and a forced expiratory volume <1 litre. In a cardiac catheterisation study of 34 patients with cystic fibrosis, these findings were associated with conspicuously raised mean pulmonary artery pressure (⩾38 mmHg) and severe cor pulmonale.[5] These correlations are not surprising in view of the pathophysiology of cystic fibrosis which involves hypoventilation caused by mucous obstruction of the airways, recurrent infections, and progressive multilobar bronchiectasis. Chronic hypoxia results, leading to pulmonary artery hypertension. Since the right ventricle is highly afterload dependent, this sustained increase in afterload ultimately results in hypertrophy and failure.[4 6 8 25–27]

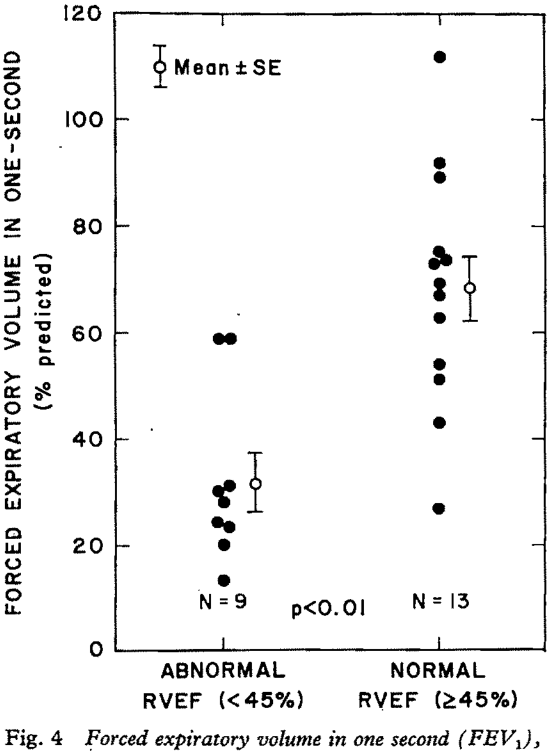

Fig. 4 *Forced expiratory volume in one second (FEV_1), expressed as a percentage of predicted in patients with cystic fibrosis. FEV_1 is significantly lower in patients with an abnormal right ventricular ejection fraction (RVEF) than in those with a normal right ventricular ejection fraction. N, number of patients; SE, standard error of the mean; p, probability.*

Although all patients were clinically compensated at the time of the study, within one year of follow-up, five of nine patients with an abnormal right ventricular ejection fraction developed respiratory failure and four of these five died with decompensated cor pulmonale. Radionuclide angiocardiography allowed identification of right ventricular dysfunction at a time when it was not appreciated by conventional clinical evaluation. Even though the abnormalities in right ventricular function were not particularly obvious, they still were a harbinger of subsequent decompensation. Thus, this technique may provide potential prognostic information. This may be particularly important because overt right heart failure usually occurs late in the course of cystic fibrosis and has been found to be a warning of imminent death. Moss *et al.*[28] reported a median survival of less than three months once right heart failure was clinically apparent. The sensitivity of radionuclide angiocardiography for detection of preclinical right ventricular dysfunction in cystic fibrosis is similar to that previously reported in patients with chronic bronchitis and emphysema. Four of nine patients with severe airways obstruction and an abnormal right ventricular ejection fraction developed decompensated cor pulmonale within one year of their original study, though none died.[12]

The electrocardiogram has not been found to be a sensitive technique for determining right ventricular hypertrophy or for following patients with cystic fibrosis.[5 9 26] Echocardiography has been applied to patients with cystic fibrosis,[9 11 29] and mild increases in right ventricular wall thickness and cavitary diameter have been shown. However, measurements of right ventricular dimensions with M-mode echocardiography, particularly in patients with obstructive lung disease, are technically difficult and unreliable in many patients.[9 30 31] As the severity of lung disease increases, the usefulness of this approach appears to decrease, making it a less desirable technique in this patient population.

In the present study, left ventricular performance was normal in all patients and at necropsy the left ventricle was normal in two patients dying with decompensated cor pulmonale. These findings are in agreement with most studies in adults with severe chronic obstructive pulmonary disease.[12 13 32–34] However, there are isolated reports of left ventricular hypertrophy and mild functional impairment in cystic fibrosis.[9 35 36]

Studies from this laboratory have established the value of radionuclide angiocardiography for assessing the response to treatment in obstructive lung disease. After aminophylline infusion, significant increases in right and left ventricular ejection fractions have been shown in patients with chronic bronchitis and emphysema.[13] With a similar technique, others have shown that right ventricular performance improves with chronic oxygen treatment.[37] Clinical trials of similar therapeutic regimens in cystic fibrosis have been hindered by a lack of sensitive, reliable, and non-invasive means of quantifying right ventricular performance. Radionuclide angiocardiography may provide a means, in addition to conventional clinical methods, for selecting appropriate patients with cystic fibrosis for treatment and for following their haemodynamic responses.

The authors thank Dr Thomas Godar for referring case 1.

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Br Heart J 1980; **43:** 481–6

Wolff-Parkinson-White syndrome type B with tachycardia-dependent (phase 3) block in the accessory pathway and in left bundle-branch coexisting with rate-unrelated right bundle-branch block

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SUMMARY A patient with Wolff-Parkinson-White syndrome type B developed 2:1 atrioventricular block resulting from the association of persistent right bundle-branch block with tachycardia-dependent (phase 3) left bundle-branch block. Electrophysiological studies disclosed the coexistence of a tachycardia-dependent (phase 3) block in the accessory pathway. This conduction disturbance was exposed, not by carotid sinus massage as in previous studies, but by pacing-induced prolongation of the interval between two consecutively conducted atrial impulses. Furthermore, the surface electrocardiogram showed, at different times, ventricular complexes resulting from: (1) exclusive atrioventricular conduction through the normal pathway without bundle-branch block; (2) predominant, or exclusive, atrioventricular conduction through a right-sided accessory pathway; (3) exclusive atrioventricular conduction through the normal pathway with right bundle-branch block; (4) exclusive conduction through the normal pathway, with left bundle-branch block; (5) fusion between (1) and (2); and finally, (6) fusion between (2) and (3)

However, QRS complexes resulting from simultaneously occurring Wolff-Parkinson-White syndrome type B and left bundle-branch block could not be identified. Future electrophysiological investigations should re-evaluate the criteria used to differentiate between true and false patterns of Wolff-Parkinson-White syndrome type B coexisting with left bundle-branch block.

The association of Wolff-Parkinson-White (WPW) syndrome, either type A or type B, with right bundle-branch block has been well recognised.[1–7] However, there are far fewer reports of the coexistence of left bundle-branch block with pre-excitation.[1 2 8–13] Even more rare is the occurrence of both right and left bundle-branch block in a patient with WPW type B.

Case report

A 62-year-old woman with WPW syndrome type B and recurrent supraventricular tachycardias was referred for electrophysiological evaluation after the appearance of right bundle-branch block and 2:1 atrioventricular block. Electrocardiograms during previous admissions had also shown pure left bundle-branch block, but exclusively when the sinus cycle lengths were shorter than 620 ms, that is when the rates were over 96/min (Fig. 1A). On the other hand, WPW type B was seen only with longer sinus cycle lengths. For example, Fig. 1B and C recorded while the rates ranged between 79 and 86/min show that the PR intervals were short (120 ms), the QRS complexes wide and of varying duration (100 to 130 ms), and the electrical axis deviated abnormally to the left (about −60°). Finally, Fig. 1D was obtained after pre-excitation had been abolished by the intravenous administration of 600 mg procainamide (given at a rate of 100 mg every five minutes). The sinus rates ranged between 79 and 83/min. The QRS complexes were narrow, there being no evidence whatsoever of left bundle-branch block.

In Fig. 1, physiological (rate - related) and pharmacological variations in the PR intervals prevented the comparison between the PJ (or PS) intervals occurring during left bundle-branch block, WPW type B, and normal conduction with narrow QRS complexes. Nevertheless, the effects of procainamide suggested that the pre-excitation complexes were fusion beats resulting from ventricular activation through both accessory and normal pathways (without left bundle-branch block in the latter). This assumption implies that the patient had a tachycardia-dependent (phase 3) left bundle-branch block.

Further evidence supporting the existence of a rate-related conduction disturbance in the left bundle-branch was obtained from intracardiac electrophysiological studies performed after development of right bundle-branch block. Thus, the first half of Fig. 2, recorded while the high right atrium was paced, shows 2:1 atrioventricular block. The first and third P waves, reaching the ventricles exclusively through the left bundle-branch, were followed 400 ms later by P waves blocked below the site from which the H deflection was recorded (presumably at both bundle-branches simultaneously).

In the beats conducted with a right bundle-branch block morphology the interval between the atrial (A) deflection of the His bundle electrocardiographic lead and the onset of ventricular (V) depolarisation (wherever it might have occurred) gave a measure of conduction time through the normal (AV node—His bundle—left bundle-branch) pathway. The duration of the corresponding AH, HV, and H right ventricular apex (RVA) intervals was 110 , 50 and 85 to 90 ms, respectively.

Since the pre-excitation had become concealed, attempts had to be made to expose, or unmask, atrioventricular conduction through the accessory pathway (Fig. 2 and 3). This was accomplished by increasing the intervals between two consecutively conducted atrial impulses by means of a single premature atrial stimulus delivered after every eighth blocked P wave. When these intervals were prolonged beyond 1000 ms, they were terminated by QRS complexes (last in Fig. 2 and in Fig. 3, left panel) which were different from those with a right bundle-branch block morphology in that: (a) lead I changed to a predominantly positive deflection (not followed by a wide S wave) with a slurring in its upstroke (delta wave); (b) the electrical axis was deviated abnormally to the left; and (c) lead V1 changed to an Rsr′ pattern (Fig. 2) or to an Rs morphology (Fig. 3, left panel). In these complexes AH remained at the control value (110 ms) but the H deflection was inscribed as the ventricles started to be depolarised by the impulse emerging from the accessory pathway. In consequence, the AV interval of 110 ms was used as a rough estimate of conduction time through the accessory pathway.[14 15]

These findings suggested that the last QRS complexes in Fig. 2 and 3, left panel, reflect fusion resulting from ventricular activation through both

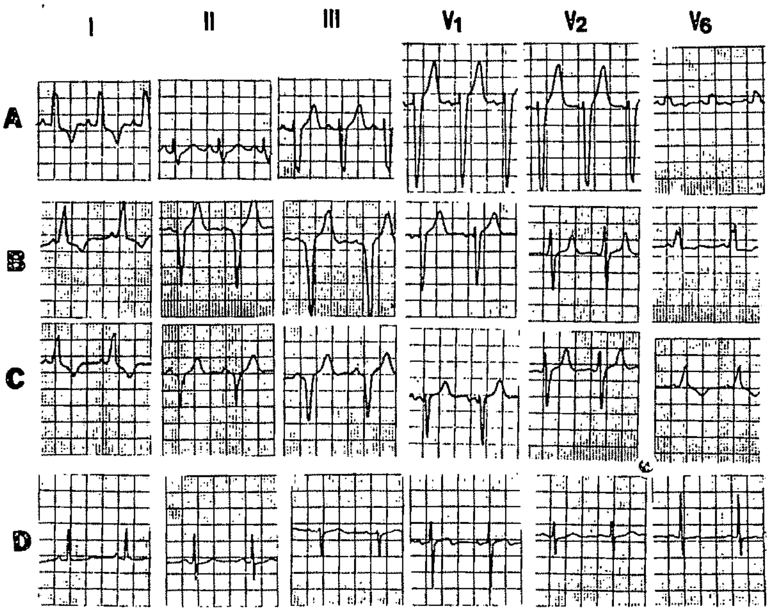

Fig. 1 *Tachycardia-dependent block in the left bundle-branch and (possibly) in the accessory pathway (A); different degrees of pre-excitation with Wolff-Parkinson-White type B morphologies (B, C) and narrow QRS complexes after procainamide (D).*

the accessory and normal pathways (with right bundle-branch block in the latter). On the other hand, the last QRS complex in Fig. 3, right panel, resulted from exclusive, or almost exclusive, conduction through the accessory pathway. It thus had a morphology similar to that in Fig. 1B.

Whenever pre-excitation occurred, the HV intervals, as well as the His-right ventricular apex (H-RVA) intervals, were shorter than in control complexes, indicating that the apex of the right ventricle was not activated by the impulse traversing the normal pathway, but by that emerging from the accessory pathway.[14, 15] Therefore, the time elapsing between the onset of the delta wave and arrival of excitation at the RVA (35 ms) was used to estimate conduction time from pre-excitated site to the apex of the right ventricle.[14, 15] Moreover, if the AV interval (of 105 ms) preceding the ventricular complexes with a delta wave indeed reflected the conduction time through the accessory pathway, then the fusion complexes in Fig. 2 and 3 can be explained by assuming that the corresponding AH interval of 110 ms still allowed certain portions of the left ventricle to be activated by the impulse descending through the left bundle-branch.[14, 15]

However, the increase of the AH interval to 140 ms which occurred in the last complex of the right panel of Fig. 3 (in turn resulting from the concealed penetration, into the atrioventricular node, of the preceding, premature, atrial beats) produced sufficient delay in the conduction of the impulse traversing the normal pathway so as to allow the impulse traversing the accessory pathway to activate all or most of both ventricles.[14, 15]

Discussion

DIFFICULTIES IN DETERMINING LOCATION OF ACCESSORY PATHWAY

The major problem in diagnosing the location of the accessory pathway in this case was related to the occurrence of pre-excitation only at very long cycle lengths (Fig. 2 and 3). Nevertheless, analysis of the surface electrocardiographic and intracardiac electrophysiological events suggested that the accessory pathway was right sided. Vectorial analysis of standard and chest leads showed that the abnormal ventricular depolarisation occurred in a superior, leftward, and posterior direction (Fig. 1 to 3). Moreover, during maximal pre-excitation the initial slurring was located partly in the left anterior quadrant and partly in the left posterior quadrant. Even in the absence of spatial vectorcardiograms these findings can be construed to indicate that the

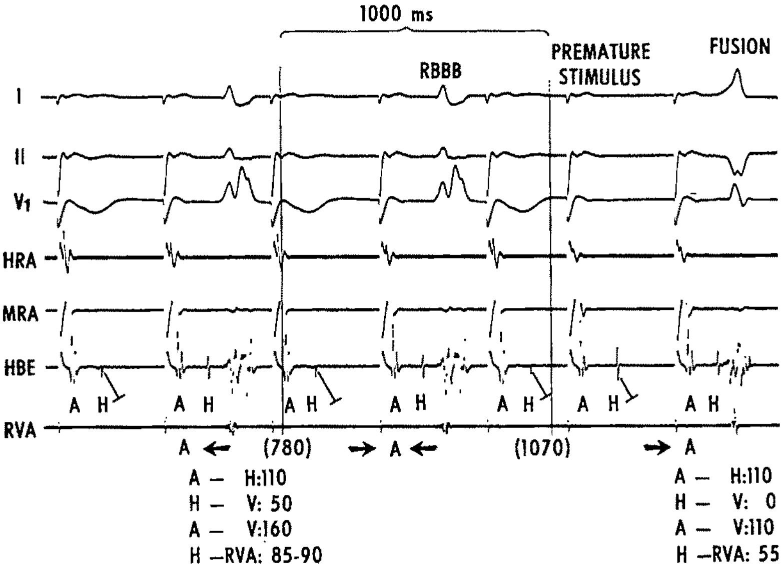

Fig. 2 *Intracardiac recordings (obtained during atrial pacing) showing: (a) pure right bundle-branch block (RBBB) in conducted impulses (first two QRS complexes); (b) 2:1 (infra-Hisian) AV block resulting from the association of persistent RBBB with tacycardia-dependent (phase 3) left bundle-branch block (LBBB); (c) tachycardia-dependent (phase 3) block in the accessory pathway; and (d) fusion resulting from the coexistence of right bundle-branch block with WPW type B (last QRS complex). Numbers between arrows refer to the interval between two consecutively conducted atrial (A) impulses. All values are expressed in ms. HRA: high right atrium; MRA: mid-right atrium; RVA: right ventricular apex; A: atrial electrogram recorded in the His bundle electrogram (HBE) lead; V: onset of depolarisation, regardless of the pathway responsible for initial ventricular activation.*

accessory pathway ended in a right-inferior, probably mid-septal, site.[16]

On the other hand, the intracardiac studies showed that the estimated conduction time between the pre-excited site and the right ventricular apex in beats with delta waves (35 ms) was similar to that previously reported in patients with WPW type B (40 to 50 ms).[15] These values were significantly shorter than those reported in patients with WPW type A (120 to 160 ms).[14]

Theoretically, the distance between the ventricular end of the accessory pathway and the recording electrodes can be determined if the conduction time, conduction velocity, and location of conduction pathways are known. Unfortunately, these indices have not been adequately defined for the human ventricles: the reported conduction times have ranged widely between 440 mm/s (in revived hearts) to 1200 mm/s (in patients with implanted left ventricular pacemakers).[17 18] In canine hearts Lewis found that the conduction velocity through the ordinary muscle of the free right ventricular wall was approximately 400 mm/s.[19]

Calculations based on these values suggest that the distance between the site of emergence from the accessory pathway and the right ventricular apex in our two cases could have ranged between 15·4 and 42 mm.

TACHYCARDIA-DEPENDENT (PHASE 3) BLOCK IN ACCESSORY PATHWAY

The absence of pre-excitation (before the development of 2:1 AV block) in all tracings showing sinus tachycardia (Fig. 1A) could have been the result of tachycardia-dependent (phase 3) block in the accessory pathway.[20] However, this assumption was not proved as electrophysiological studies were not performed.

In our opinion the diagnosis of the conduction disturbance under consideration cannot always be made exclusively from the surface electrocardiogram since multiple factors can produce false patterns of tachycardia-dependent (phase 3) block in the accessory pathway.[21] Foremost among these are the differences in conduction time through normal pathway and anomalous pathway.

Disappearance of pre-excitation at relatively high rates may simply be an expression of a sympathetic enhancement of AV nodal conduction without any change in the physiological properties of the accessory pathway. In addition, this phenomenon has also been ascribed to a shift in the site of impulse initiation, to differential intra-atrial delays, and to changes in the site and mode of entry into the AV node and accessory pathways.[21 22] Similarly, the exposure of pre-excitation during sinuatrial slowing produced by carotid sinus massage[20] may be explained entirely by vagal-induced AV nodal block of high degree.

The method used to unmask the pre-excitation in Fig. 2 and 3 was different from that used by Przybylski *et al.*[20] Fig. 2 and 3 also show that the occurrence of pre-excitation at long cycle lengths was related to: (a) the duration of the phase 3 block in the accessory pathway; and (b) differences in conduction time through the latter and through the normal pathway.

RIGHT BUNDLE-BRANCH BLOCK IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

The association of right bundle-branch block with WPW type A, or type B, has been well recognised and thoroughly discussed.[1–7]

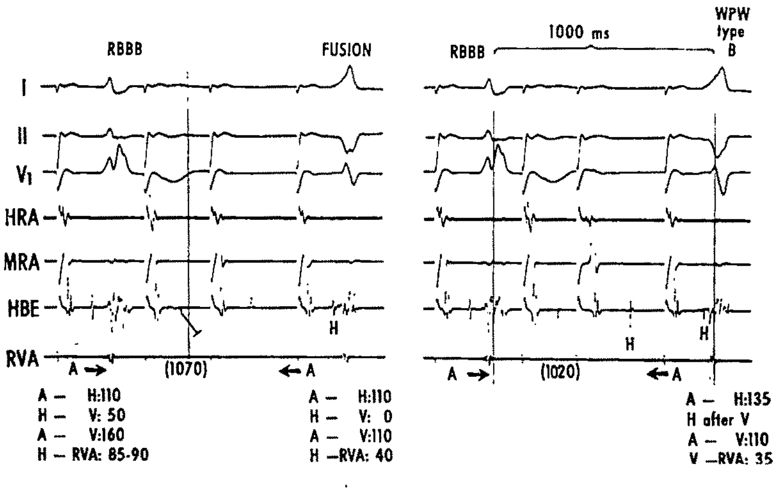

Fig. 3 *Atrial pacing with: (a) pure right bundle-branch block in conducted impulses (first QRS complex in the left, and in the right panel); (b) 2:1 AV block resulting from the association of persistent right bundle-branch block and tachycardia-dependent (phase 3) block in the accessory pathway; (d) fusion resulting from the coexistence of right bundle-branch block with WPW type B (second QRS complex in the left panel); and (e) ventricular complex (last in the right panel) with a pure, or almost pure, WPW type B morphology.*

LEFT BUNDLE-BRANCH BLOCK IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME TYPE A

In contrast, as recently emphasised by Krikler *et al.*[13] fewer reports have dealt with left bundle-branch block coexisting with WPW type A.[10–12] Moreover, Krikler *et al.*[13] also reviewed the published reports and presented information from two personal cases in which electrophysiological studies were performed.

RATE-UNRELATED LEFT BUNDLE-BRANCH BLOCK IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME TYPE B

In the very few reports dealing with this combination, the diagnosis was made by electrocardiographic and (or) vectorcardiographic analysis. However, as stated by Krikler *et al.*[13] 'final proof requires electrophysiological techniques'. Therefore, it is possible to question some tracings (showing short PR intervals and *very* wide QRS complexes) which were attributed to WPW type B coexisting with left bundle-branch block either because 'after the endpoint of pre-excitation there was further prolongation of the QRS',[23] or because 'horizontal QRS loops with leftward and posteriorly oriented delta and maximal vectors were followed by additional mid-delays and slurrings'.[2]

In the light of recently acquired information they can be explained by assuming exclusive AV conduction through a right-sided accessory pathway, without necessarily postulating the concomitant existence of left bundle-branch block.[16] This accessory pathway could be atrioventricular ('Kent') as well as fasciculoventricular ('Mahaim'). Electrophysiological verification is essential, because similar patterns can occur when the ventricles are activated almost simultaneously by impulses emerging from a right anterior (parietal or septal) accessory pathway and from the right bundle-branch (in cases where the left bundle-branch is completely blocked). This was shown in the studies of Latour and Puech[24] and Mendoza *et al.*[25] where simulated (catheter-induced) right septal pre-excitation was produced in patients with left bundle-branch block. The ventricular complexes resulting from iatrogenic right ventricular pre-excitation were as wide as (but of different morphology from) those occurring when sinus rhythm (with left-bundle-branch block) was present.

TACHYCARDIA-DEPENDENT (PHASE 3) LEFT BUNDLE-BRANCH BLOCK IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME

As far as we know there is only one reported case where the authors postulated that this conduction disturbance might have been present in a patient with WPW syndrome. According to Krikler *et al.*[13] the left bundle-branch block occurring in one of the cases (with WPW type A) reported by Pick and Fisch[1] was probably tachycardia-dependent. In our patient this diagnosis was possible because, regardless of the underlying electrophysiological mechanism, pre-excitation did not occur during sinus tachycardia (Fig. 1A). Furthermore, left bundle-branch block was not seen when pre-excitation was abolished with intravenous procainamide while the rate was slower (Fig. 1D). After development of persistent right bundle-branch block, the tachycardia-dependent (phase 3) left bundle-branch block naturally coexisted with the former, thus being manifested as infra-Hisian (bilateral bundle-branch) block in alternate beats (Fig. 2 and 3).

VARYING QRS MORPHOLOGIES

The patient discussed in this communication is unique, in that she had, at one time or another, ventricular complexes representing: (a) exclusive normal (AV node-His Purkinje) pathway conduction without bundle-branch block (Fig. 1D); (b) predomonant or exclusive AV conduction through a right-sided accessory pathway (Fig. 3, right panel); (c) pure right bundle-branch block (Fig. 2 and 3); (d) pure left bundle-branch block (Fig. 1A); (e) fusion complexes resulting from the coexistence of (a) and (b) (Fig. 1B and C); and (f) fusion complexes resulting from the coexistence of (b) and (c) (Fig. 2 and 3). However, fusion caused by simultaneously occurring WPW type B and left bundle-branch block could not be identified, and this association still requires further electrophysiological evaluation.

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Requests for reprints to Dr Agustin Castellanos, Division of Cardiology (D-39), University of Miami School of Medicine, PO Box 016960, Miami, Florida 33101, USA.

Br Heart J 1980; **43:** 487–9

Giant cell arteritis of coronary arteries causing myocardial infarction

J F MARTIN, C KITTAS, D R TRIGER

From the Department of Medicine, University of Sheffield, Floor M, Hallamshire Hospital, Sheffield

SUMMARY A case of giant cell arteritis involving the coronary arteries and causing thrombosis and myocardial infarction is described. IgM deposits in the affected arteries were demonstrated by an immunoperoxidase technique.

Death from giant cell arteritis alone is rare and is mainly the result of ruptured aorta (Östberg, 1973; Klein *et al.*, 1975). Arteritic involvement of the coronary arteries is even more rare, there being 6 published cases (Morrison and Abitol, 1955; Ainsworth *et al.*, 1961; Östberg, 1973; Klein *et al.*, 1975). Myocardial infarction has been claimed in 2 cases (Morrison and Abitol, 1955; Ainsworth *et al.*, 1961), but the reports give no evidence of a causal link between the arteritis and myocardial infarction. We describe a case of giant cell arteritis with histologically proven involvement of the coronary arteries causing thrombosis, myocardial infarction, and death.

Case report

A 77-year-old housewife complained of central chest pain, radiating to her left arm and neck, initiated by exertion and lasting 2 hours. For 9 months previously she had malaise and weight loss. For 3 months she had suffered severe burning headaches and jaw claudication. On examination she was pale and had very tender temporal arteries. Her eyes were normal. A clinical diagnosis of giant cell arteritis was made. ESR was 85 mm/h, Hb 11·1 g/100 ml. Electrocardiogram was normal. Treatment with prednisolone 60 mg daily was begun and the next day she felt better. On the third day after admission she again complained of severe chest pain and collapsed. Ventricular fibrillation was converted to sinus rhythm by DC shock. Electrocardiogram showed an anterior myocardial infarction. Intravenous lignocaine controlled ventricular ectopic beats, but she died 6 hours later after an episode of asystole.

Necropsy showed the aorta and coronary vessels to be free from atheroma. The anterior descending branch of the left coronary artery was completely occluded by a thrombus 3·6 cm from the ostia. A large area of the anterior and anteroseptal walls of the left ventricle was infarcted. Histological examination showed changes of giant cell arteritis, in the cerebral, coronary, and temporal arteries; the latter being more severely damaged. Sections taken from the anterior descending branch of the left coronary artery showed occlusion of the lumen by a thrombus superimposed on active arteritic changes (Fig. 1). Sections stained by the immunoperoxidase method (Heyderman and Munro-Neville, 1977) for immunoglobulins, showed strong cytoplasmic and weaker granular extracellular staining for IgM adjacent to the elastic lamina (Fig. 2). The cells positive for IgM were plasma cells and a few macrophages. There was no histological involvement of the aorta.

Discussion

Angina in a patient with temporal giant cell arteritis is most likely to be caused by unrelated atheromatous changes in the coronary tree. However, involvement of the latter by giant cell arteritis should be borne in mind in view of its potential reversibility with prednisolone. Our patient died of coronary artery occlusion after receiving an adequate dose of prednisolone for 3 days; 3 of the reported cases of aortic rupture also died while receiving adequate doses of prednisolone and after symptomatic improvement (Klein *et al.*, 1975). We believe that these results do not reflect the irreversibility of the arteritic changes but underline the necessity of early diagnosis and treatment before the establishment of lesions such as thrombosis of the coronary arteries or weakness of the aortic wall,

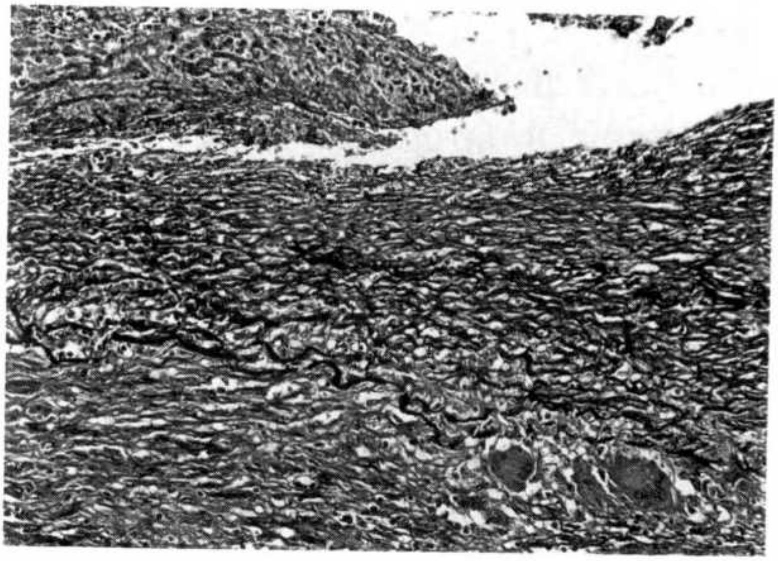

Fig. 1 *Section through the coronary artery showing two giant cells in the bottom right-hand corner, and in the top left-hand corner thrombus is adherent to the vessel wall* (× 100).

leading to myocardial infarction and ruptured aorta, respectively.

Immunoglobulins have been found using immunofluorescence, in temporal arteries affected by giant cell arteritis (Liang *et al.*, 1974); it has also been suggested that the demonstration of IgM should be the criterion of diagnosis in temporal arteritis (Bonnetblanc *et al.*, 1978). We have here shown IgM in both the temporal and the coronary arteries using an immunoperoxidase method. In the diagnosis of giant-cell arteritis this technique may be of greater value than immunofluorescence as it can be applied to formalin-fixed, paraffin-embedded material.

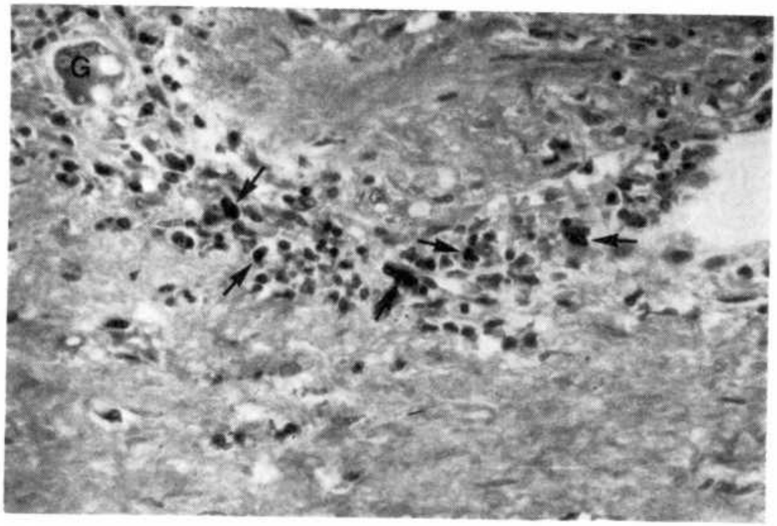

Fig. 2 *Section through the coronary artery showing chronic inflammatory infiltrate. A giant cell (G) is shown. The arrows indicate plasma cells with strong cytoplasmic immunoperoxidase staining for IgM. Weak extracellular IgM deposits are also present* (× 400).

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Br Heart J 1980; **43**: 490–1

Papilloedema and hepatic dysfunction apparently induced by perhexiline maleate (Pexid)

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SUMMARY A patient developed papilloedema and hepatic dysfunction while being treated with perhexiline maleate. These later regressed when the drug was withdrawn. Patients should be monitored for these potentially serious side-effects while on this drug.

Perhexiline maleate (Pexid), a drug introduced for the prophylaxis of angina pectoris, has been implicated in the development of peripheral neuropathy,[1] ataxia,[2] myopathy,[3] and papilloedema.[4] We describe here a patient who developed papilloedema and abnormal liver function while on the drug, these abnormalities subsiding after it was withdrawn.

Case report

A 48-year-old man presented in September 1978 with a complaint of staggering to the right, nausea, vomiting, and early morning headaches for six weeks. There was no history of recent excessive alcohol intake. He was known to have been severely hypertensive since 1966. Enucleation of the left eye had been performed after trauma in 1975. He had had severe angina pectoris from 1977, for which coronary artery bypass surgery was performed in September 1977. After a myocardial infarction in December 1977, the angina, which had been relieved by operation, recurred, and in April 1978 perhexiline maleate (Pexid) 200 mg twice daily was prescribed in addition to the then current therapy of bumetanide 2 mg daily, amiloride 10 mg twice daily, sorbitrate 10 mg four times daily, propranolol 320 mg twice daily, and hydralazine 25 mg twice daily.

On initial examination the blood pressure was 150/90 mmHg. There was no evidence of cardiac failure. He had incoordination of the right leg on heel-shin testing, and unsteadiness of gait, tending to stagger to the right. Papilloedema was seen in the right eye. Fluorescein angiography disclosed distinct leakage of fluorescein from the disc, especially in the later phases from five minutes onwards (Fig.). Visual field testing showed an enlarged blind spot. His visual acuity, however, remained excellent at 6/5 (corrected). Serum asparate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH) were obviously raised at 585, 1185, and 890 U/l; these had been 16, 26, and 375 U/l, respectively, in December 1977 (normal ranges <42, <55, and <500). Hepatitis B antigen was negative. Haemoglobin was 16·1 g/dl. Serum electrolytes and urea were normal. Electrocardiograms showed no change from previous records. Skull *x*-ray, electroencephalogram, isotope brain scan, and computerised axial tomography of the brain were normal.

As his new symptoms and signs were thought probably to result from perhexiline maleate toxicity, this drug was withdrawn. Six weeks later the patient reported improvement of symptoms, the papilloedema and ataxia were less distinct, and a repeat fluorescein angiogram showed less leakage of dye from the disc (Fig.). AST, ALT, and LDH had all become normal (21, 19, and 375 U/l, respectively).

Discussion

One previous case of hepatic dysfunction together with papilloedema has been described in a patient receiving perhexiline,[2] and several cases of papilloedema have been described in association with the drug.[1 3 4] In our patient the symptoms and signs improved within six weeks of withdrawal of the drug. Perhexiline, therefore, seems likely to have been the offending agent.

The mechanisms involved are unclear. In one case a raised cerebrospinal fluid (CSF) pressure was shown by lumbar puncture.[2] However, in a more recent report the CSF pressure was normal but the

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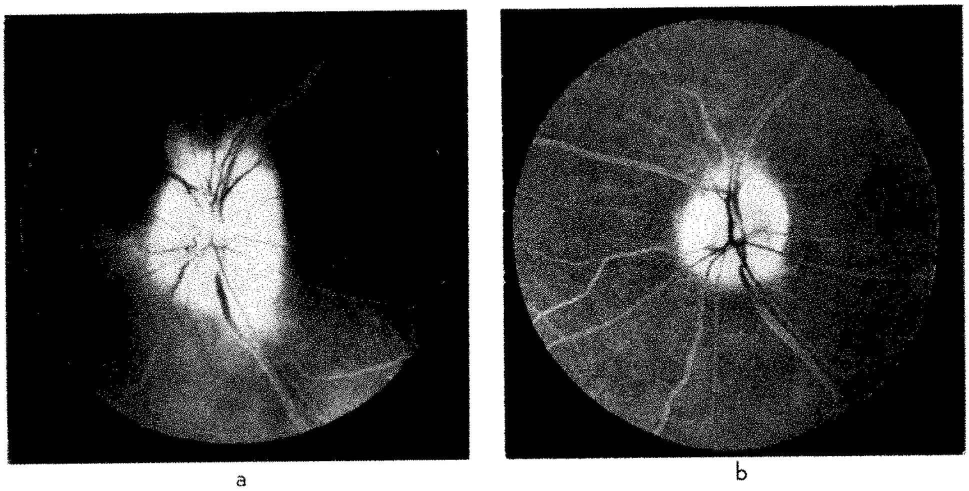

a b

Fig. *Fluorescein angiograms of the fundus shown at 10 minutes after injection of dye: (a) in September 1978 while on perhexiline maleate shows gross leakage of dye, while (b) taken in November 1978 shows almost complete resolution.*

protein concentration raised.[4] Lumbar puncture was not performed in our patient because of the possible risk involved. The cause of the hepatic dysfunction also remains undetermined.

In the present case, symptoms began four months after the treatment was started. This is sooner than in previous reports,[1-4] in which patients developed symptoms after at least 10 months' therapy. The more rapid onset here may have been a result of our using the highest recommended dose. The clinical features of toxicity normally resolve, as in the present case, but in one previous patient visual acuity was still impaired two years after stopping the drug.[2]

We suggest that perhexiline maleate be prescribed only after other medical treatments for angina have failed and that, when it is given, hepatic function tests and ophthalmological screening should be performed at regular intervals.

We should like to thank Drs A F Lever and J I S Robertson for permission to report this patient who was under their care and also for their help and encouragement in writing this paper. We should also like to thank Professor J A Simpson who supervised the neurological investigations.

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Requests for reprints to Dr A B Atkinson, MRC Blood Pressure Unit, Western Infirmary, Glasgow G11 6NT.

Notices

Br Heart J 1980; **43**: 492

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An international symposium devoted to the interaction between prostaglandins and the cardiovascular system will be held in Wilrijk (Antwerp, Belgium), from 1–3 December 1980. This symposium is sponsored by the European Society for Cardiology. The deadline for submitting an abstract is 1 June.

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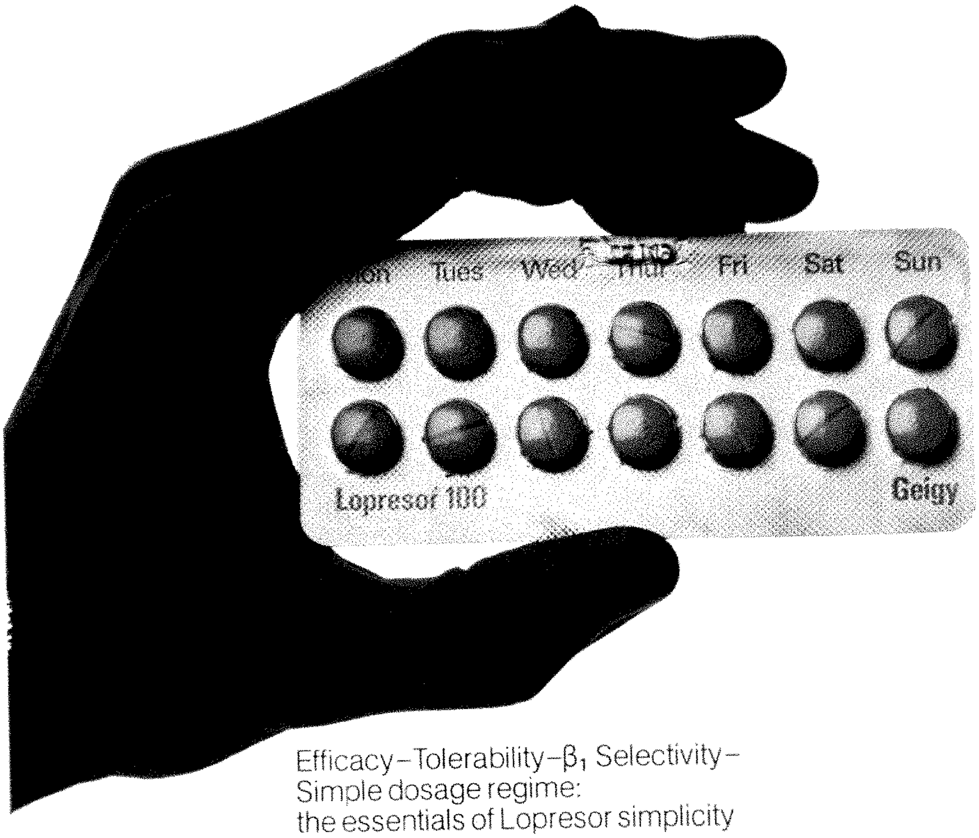

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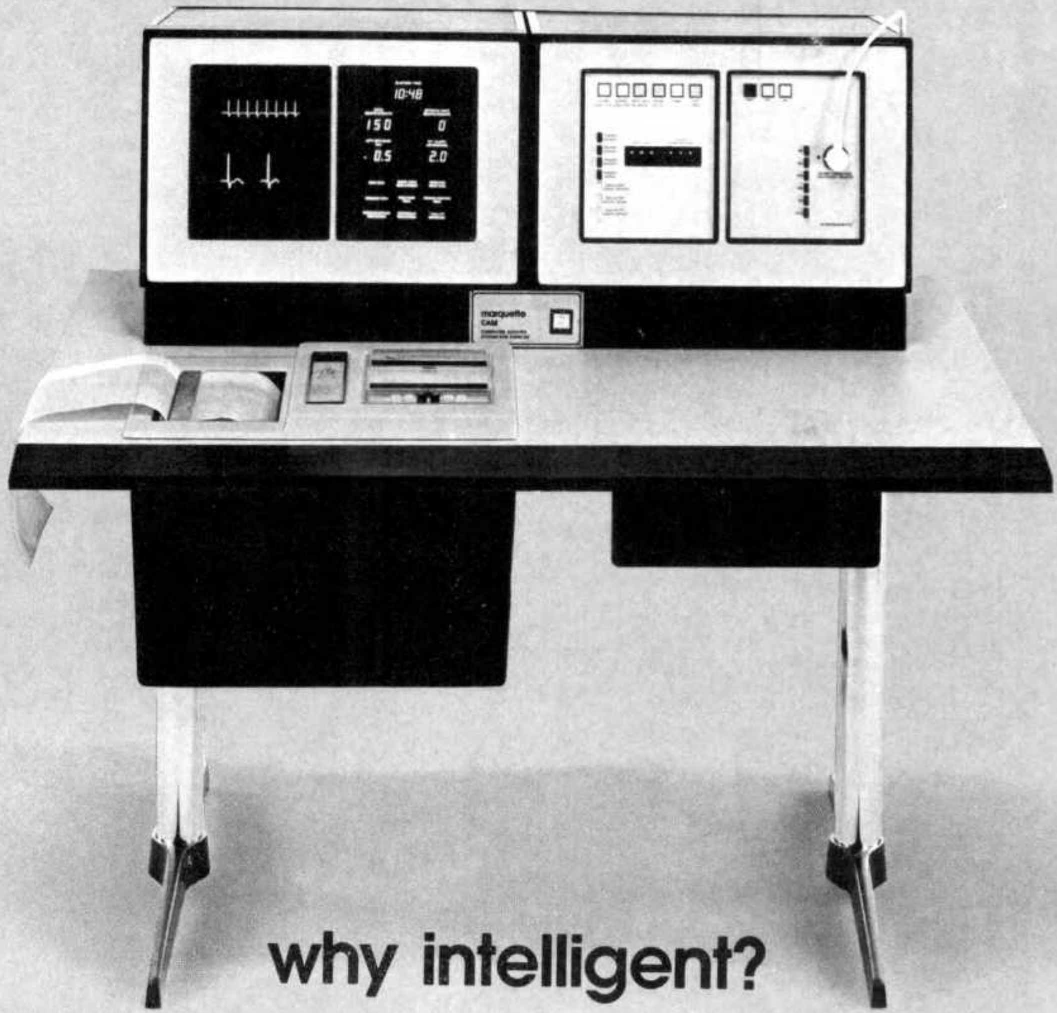

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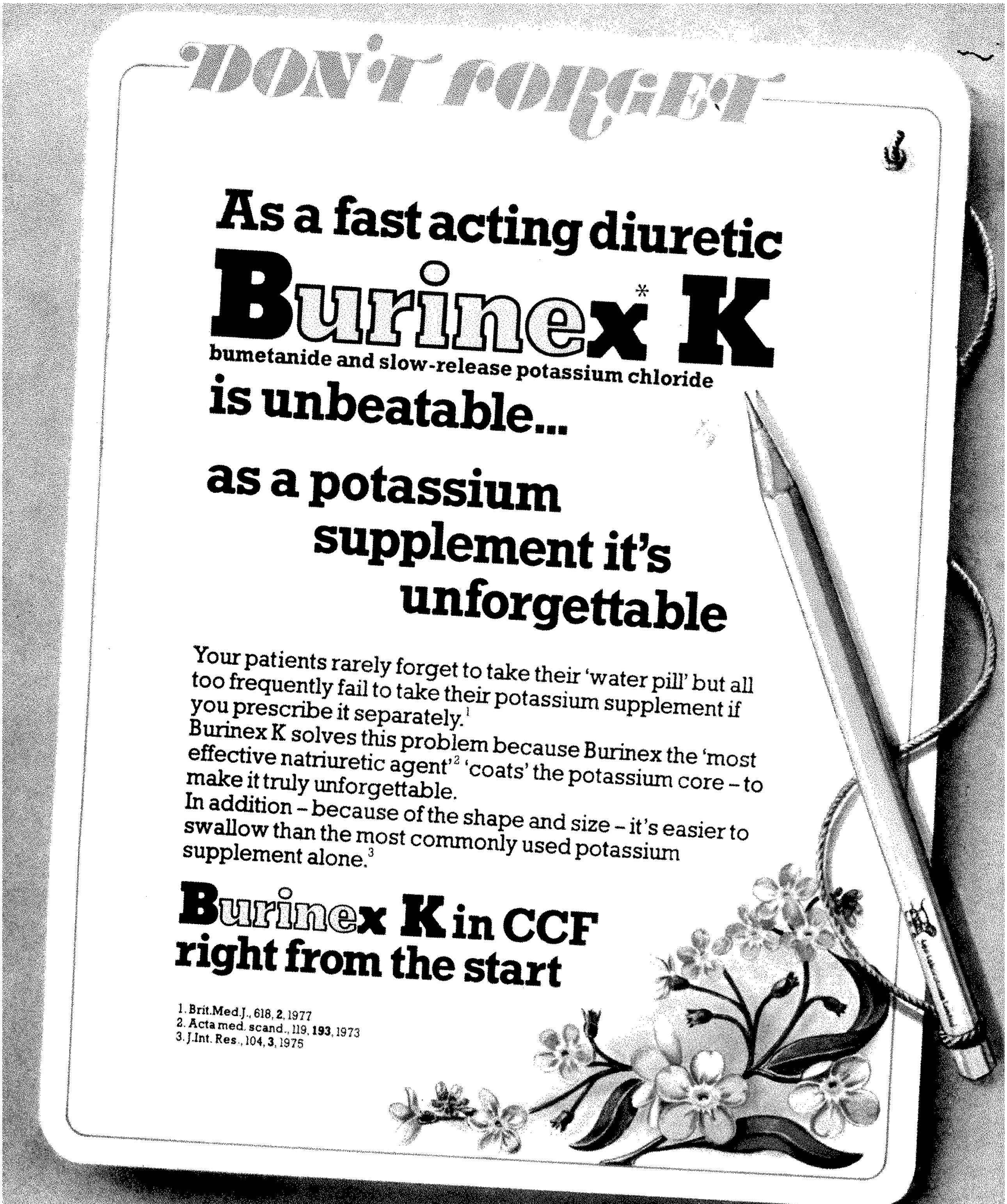

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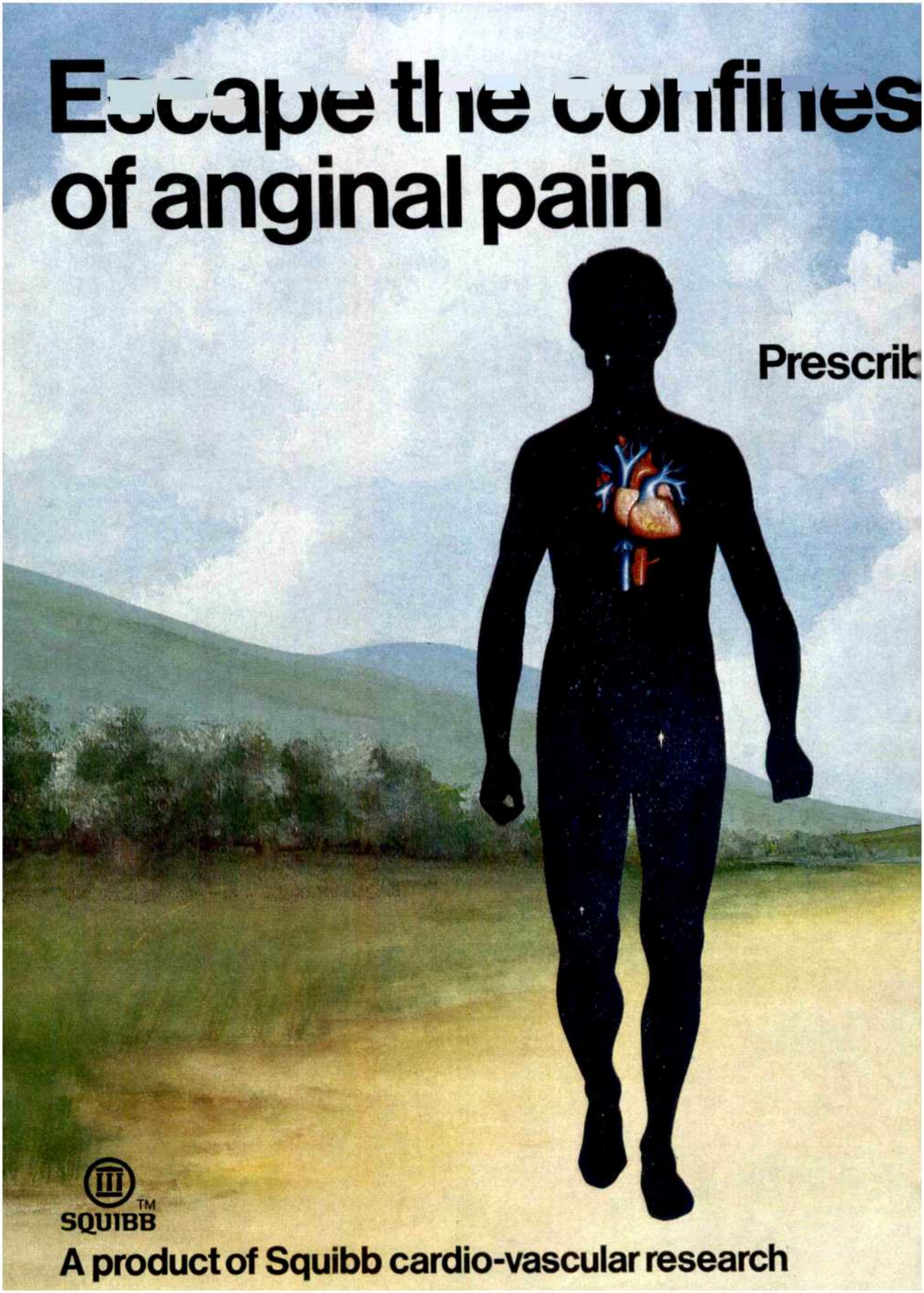
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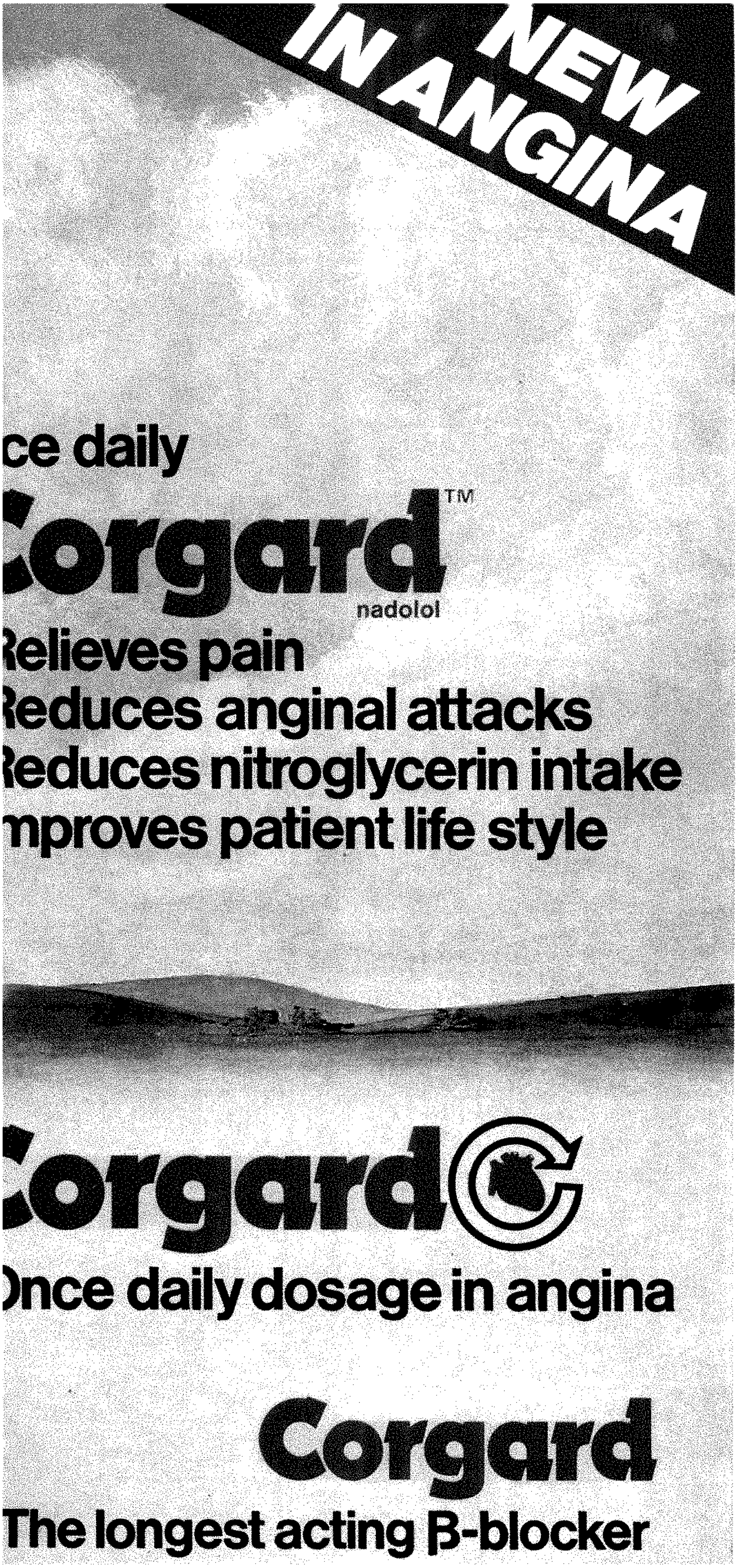
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Contra-indications
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Warnings
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Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus.
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Legal category
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Product Licence Numbers
80 mg - 0034/0186
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Package quantities
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Average daily cost of treatment 15p per day.

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CONTRA-INDICATIONS, WARNINGS ETC.

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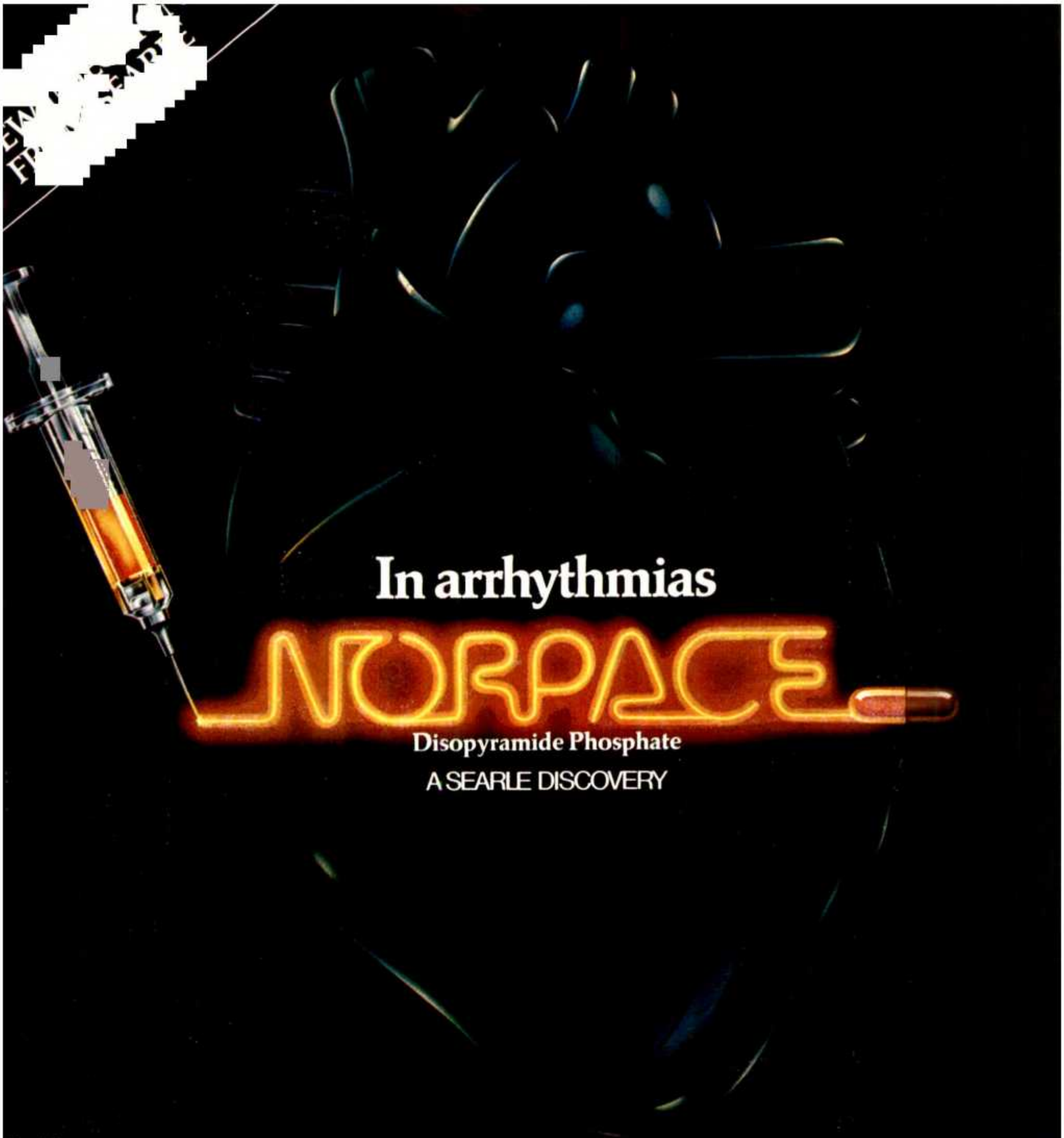

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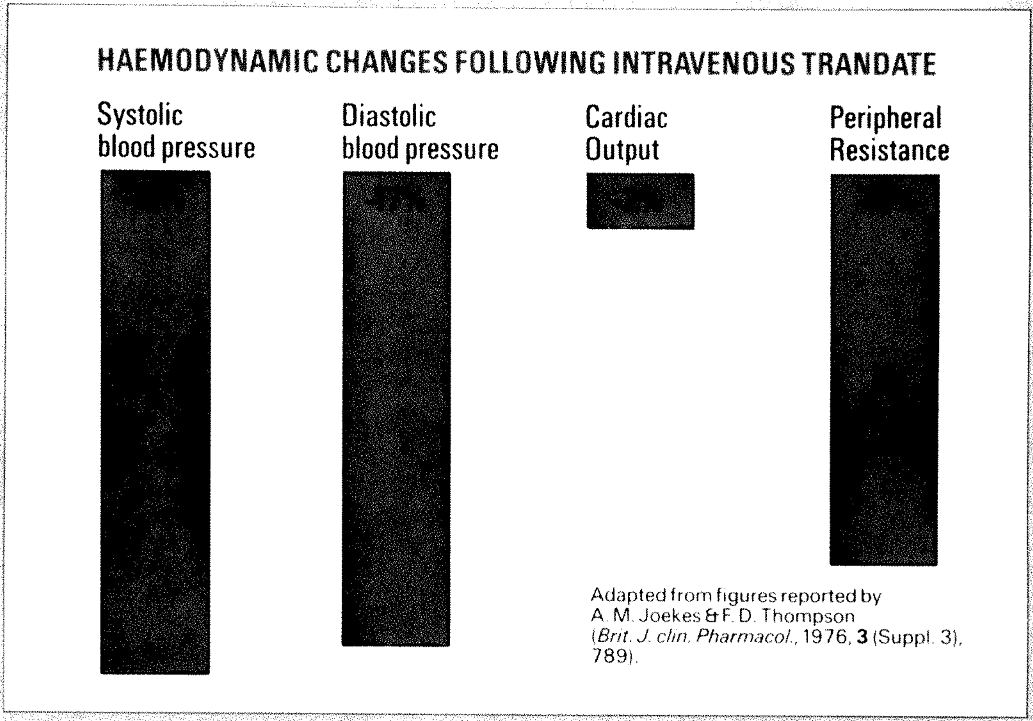

Adapted from figures reported by A. M. Joekes & F. D. Thompson (*Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 789).

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Subsequent treatment can be continued with the same drug given orally

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(Rønne-Rasmussen, J. O. et al, *Brit. J. clin. Pharmacol.*, 1976, **3** (Suppl. 3), 805)

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(Altman, M., *J. Pharmacotherapy*, 1978, **1**, 208)

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For information on the use of Trandate with other drugs or for transfer to Trandate from other antihypertensive agents, see respective Data Sheets.

CONTRA-INDICATIONS, WARNINGS, ETC.

Trandate should not be given to patients with uncontrolled or digitalis-resistant heart failure, or with atrioventricular block. Caution is necessary in asthmatic patients or others prone to bronchospasm. Patients with severe liver damage will probably require lower doses of Trandate than usual. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.

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Warning: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the drug was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.

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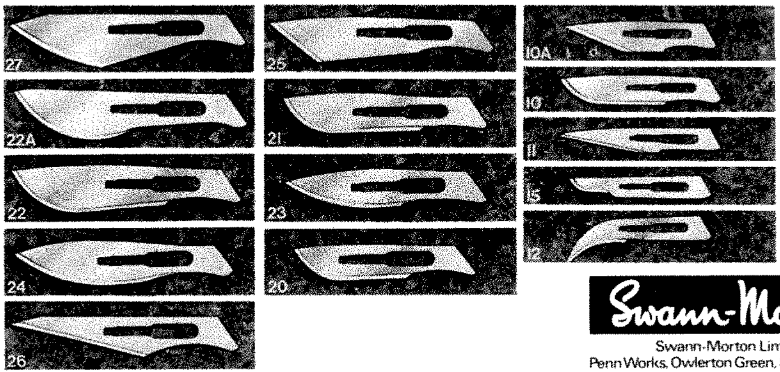

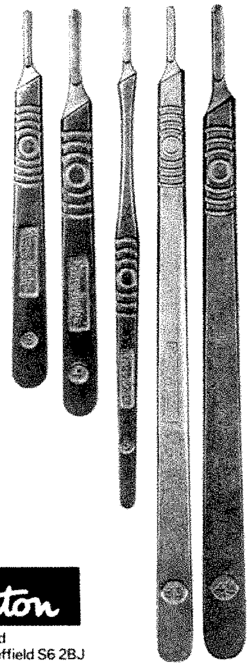

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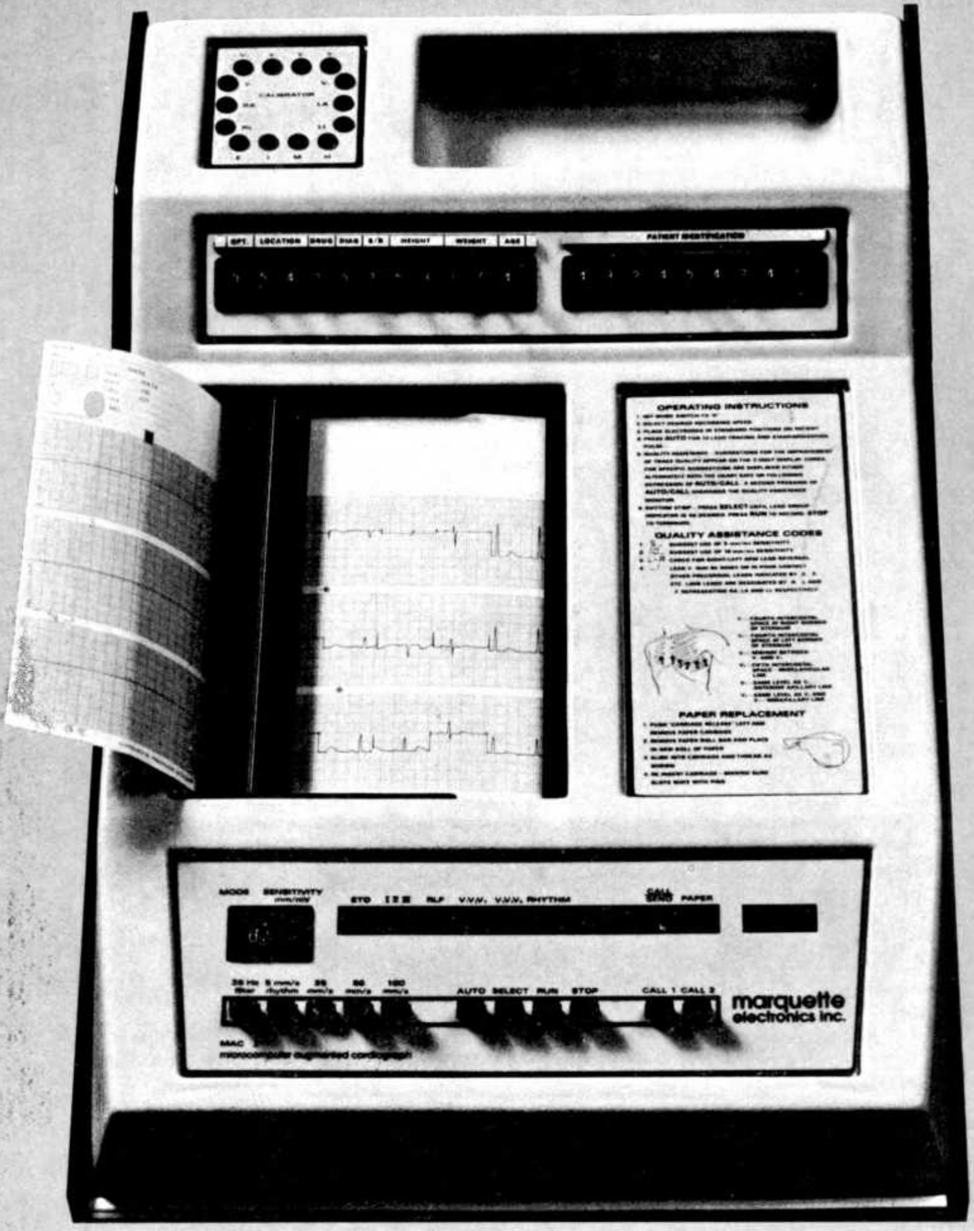

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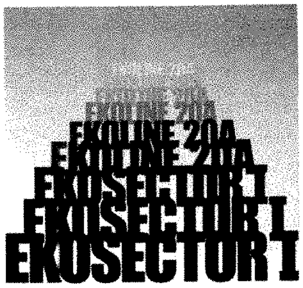

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Br Heart J 1980; **43**: 493–8

Myocardial infarction with normal coronary angiogram

Possible mechanism of smoking risk in coronary artery disease

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SUMMARY The coronary angiograms of 120 consecutive patients under 40 years of age were examined. Ten new cases of myocardial infarction with normal coronary arteriogram were identified (group 1) and compared with 30 cases of myocardial infarction and obstructive coronary disease (group 2). Heavy cigarette smoking was the sole major risk factor in group 1. Patients in group 2 smoked as well but most also had hypercholesterolaemia or hypertension. Pre- and postinfarction angina was rare among the patients with myocardial infarction and normal coronary arteriogram, and recanalisation after smoking-induced thrombotic occlusion is thought to be the most likely mechanism. Smoking-induced thrombosis is only likely to be recognised in special circumstances, when it develops in apparently normal coronary arteries, is followed by recanalisation, and is complicated by infarction as a permanent marker of previous obstruction to regional myocardial blood flow. Thrombotic occlusion of a "normal" coronary artery without recanalisation will only be recognised when infarction is fatal. If smoking can predispose to thrombosis in "normal" coronary arteries, it may be even more likely to accelerate thrombosis in atheromatous coronary arteries. The importance of recognising group 1 may well be in relation to the much commoner group 2.

The apparent paradox of well-documented myocardial infarction with a subsequently normal coronary arteriogram is no longer regarded as a rarity.[1–3] Rosenblatt and Selzer[4] reviewed the clinical features in six of their own cases and 19 other published cases and emphasised the absence of preinfarction syndrome, the absence of postinfarction angina, and the better prognosis. This study was undertaken to examine the clinical features and risk factors which distinguish those patients with myocardial infarction and a normal coronary arteriogram from those whose infarction was associated with obstructive coronary disease before the age of 40. We examined this "young" group because causal factors may be more readily identified when they have exerted their effect at this early age.

Subjects and methods

We examined 120 consecutive selective coronary arteriograms in patients under the age of 40. These studies were carried out between 1973 and 1977. There were 11 patients with major segmental left ventricular akinesia and no recognisable narrowing greater than 50 per cent of any major coronary vessel, and 30 patients with major segmental left ventricular akinesia and obstructed coronary arteries. The medical records of these 41 patients were reviewed for clinical documentation of myocardial infarction, clinical course, and presence of risk factors. The criteria for documented myocardial infarction were a typical history, enzyme release, and the subsequent development of Q waves on the electrocardiogram. One patient from group 1, an adolescent with a traumatic myocardial infarction, was excluded, leaving 40 patients for further analysis. The clinical features recorded were the presence or absence of pre- and postinfarction angina, late death, and the major risk factors: raised cholesterol, cigarette smoking, and hypertension.

Results

The summary of the findings in group 1, the 10 patients with myocardial infarction and norma

Received for publication 14 June 1979

Table 1 *Features of 10 cases of myocardial infarction with normal coronary arteriogram*

Case	*Age/sex*		*Preinfarction angina (duration)*	*Postinfarction angina*	*Cigarettes per day*	*Cholesterol (mg/100ml)**	*Time from infarction to angiography (months)*
1	40	F	—	— (after aneurysmectomy)	25	230	6
2	37	M	—	—	40	195	36
3	23	M	—	— (after aneurysmectomy)	20	140	18
4	29	M	+ (4 months)	—	20	220	3
5	33	M	—	—	20	190	12
6	38	M	—	—	60	160	18
7	31	M	—	—	10	217	3
8	26	F	—	—	25	225	12
9	29	M	+ (3 days)	—	0	190	3
10	25	M	—	+ (3 months) – (now)	15	200	5

+ = Present. – = Absent. * Cholesterol 1 mg/100 ml ≈ 0·025 mmol/l.

coronary arteriogram, is presented in Table 1. Eight of the patients were men and two were women, age range 23 to 40 years (mean 31 years). Angiography was performed three to 36 months (mean 23 months) after myocardial infarction. None of the 10 patients had raised cholesterol or hypertension but nine were cigarette smokers, with a mean cigarette consumption of 25 cigarettes per day; one was a non-smoker. None of the patients was diabetic. Eight of the patients gave no history of chest pain before myocardial infarction. One patient had had typical exertional angina for four months and another patient gave a three-day history of exertional angina before myocardial infarction. After initial infarction all patients but one stopped smoking and that patient had two subsequent myocardial infarctions without pre- or postinfarction angina. Two patients had angina and breathlessness after infarction which went after successful left ventricular aneurysmectomy. Another patient had exertional angina for three months after infarction and has been asymptomatic for five years since then; the remaining six patients have had no angina after infarction. All the patients are alive after a mean follow-up period of four years from the time of myocardial infarction.

In group 2 there were 30 patients with myocardial infarction and an abnormal coronary arteriogram, 11 women and 19 men, age range 25 to 40 years (mean 33 years). Angiography was performed one to 52 months (mean 30 months) after myocardial infarction, but in only one patient within four months. All 30 patients with myocardial infarction and an abnormal coronary arteriogram had at least one major risk factor: 25 had raised cholesterol, 8 patients had previously documented hypertension, and 22 were cigarette smokers. Cigarette smoking was the sole major risk factor in five of the patients. The mean serum cholesterol level was 340 mg/100 ml (8·8 mmol/l) and the mean cigarette consumption was 18 cigarettes per day. Twenty-two of the patients had had preinfarction angina for between one week and five years before myocardial infarction and 20 of the patients had postinfarction angina. After initial infarction 10 of the 22 cigarette smokers stopped smoking. Six of the patients had a subsequent myocardial infarction which was fatal in two cases; five of these patients were still smoking at the time of reinfarction. There were four other deaths in group 2: in two this resulted from documented arrhythmias, in one from presumed arrhythmia, and in one from left ventricular failure, after a follow-up period of two to eight years (mean five years) from the time of infarction.

In Table 2 the risk factors in patients in group 1 with myocardial infarction and a normal coronary arteriogram are compared with those in group 2 with myocardial infarction and an abnormal coronary arteriogram. Only one patient in group 1 had no major risk factor. No patient in group 1 had a raised cholesterol or hypertension whereas 80

Table 2 *Comparison of risk factors in patients with myocardial infarction and normal coronary arteriogram (group 1) and those with occlusive coronary artery disease (group 2)*

	Group 1 (10 patients)	*Group 2 (30 patients)*
No risk factor	1	0
Raised cholesterol	0	25
Hypertension	0	8
Cigarette smoking	9	22

per cent of the patients in group 2 had a raised cholesterol and 25 per cent had hypertension. Cigarette smoking was the sole major risk factor in nine of the 10 patients in group 1 and in five of the 30 patients in group 2. It is apparent that cigarette smoking was the common risk factor; nine of the 10 patients in group 1 and 22 of the 30 patients in group 2 were cigarette smokers.

Discussion

The occurrence of myocardial infarction must imply critical curtailment of the nutrient blood supply to the infarcted area at the time of necrosis regardless of the subsequent angiographic state of the coronary vessels. Though microvascular disease has been suggested it has not been shown and

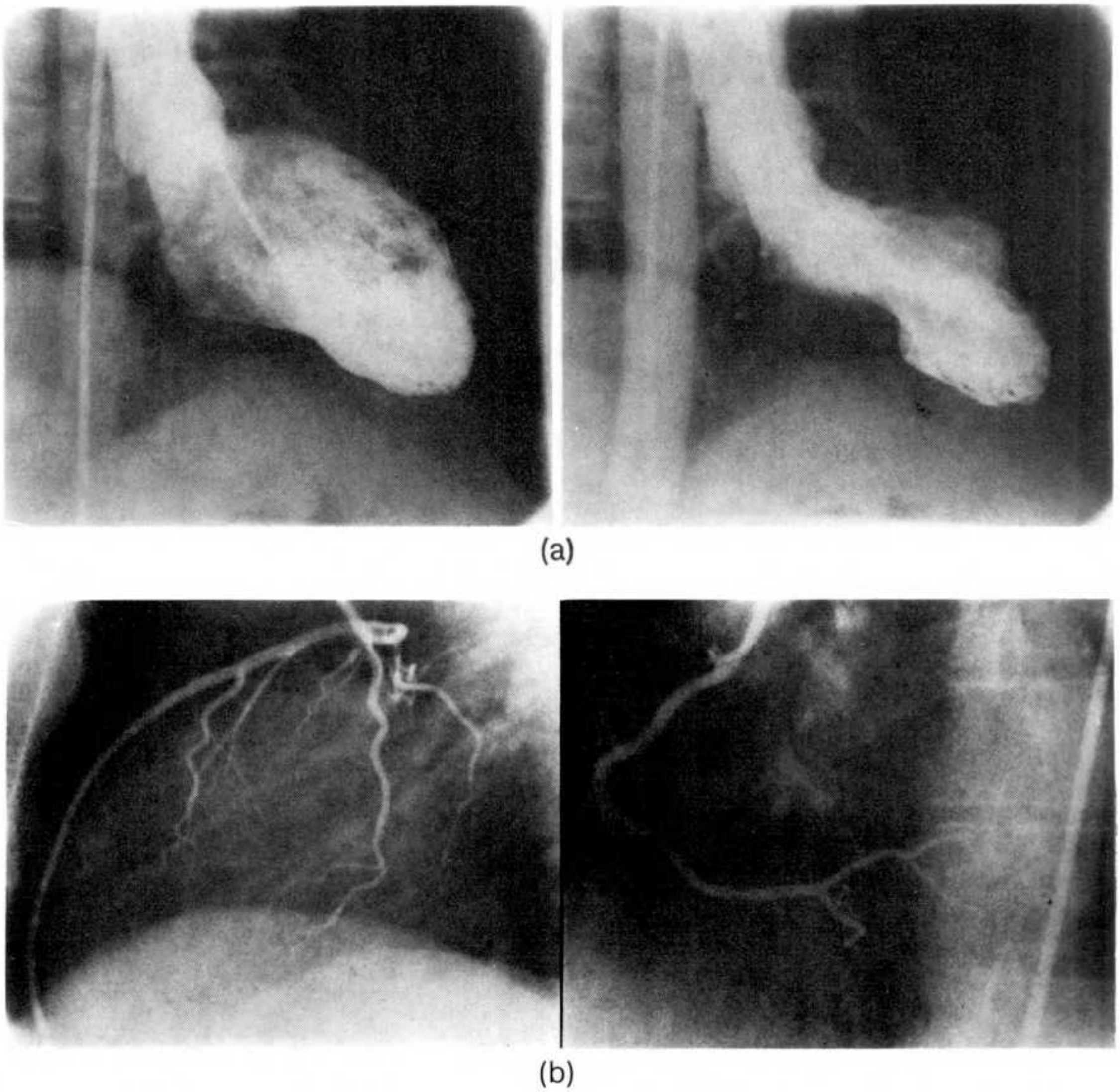

Fig. *Case 6 (Table 1) with three documented myocardial infarctions.* (a) *Diastolic and systolic frames from left ventriculogram (right anterior oblique projection) showing anterior and inferoapical akinesia.* (b) *Lateral views of left and right coronary arteries which are angiographically normal.*

would in any case be unlikely to cause circumscribed infarction within the territory of a major coronary artery.

Coronary arterial spasm producing myocardial infarction has recently been reported and is well documented.[5] It has been shown, however, that patients with variant angina possibly caused by spasm of normal coronary arteries have a distinctive clinical pattern characterised by recurrent, usually nocturnal, attacks of chest pain.[6] The reported cases of myocardial infarction with angiographic visualisation of the arteries in spasm followed this same clinical course, which was different from that of the patients we have presented. None of our patients in either group 1 or group 2 had any clinical, electrocardiographic, or angiographic features to suggest coronary spasm.

It is possible that an atheromatous coronary occlusion which has caused myocardial infarction may be missed at subsequent coronary arteriography. Technical factors such as the equipment, the number of views taken, the quality of the film, and the skill of the interpreter are all sources of possible error; though an occlusive lesion can be missed, we scrutinised the major artery of supply of the infarcted territory with special care in all our angiograms.

The most attractive hypothesis is that infarction resulted from thrombotic occlusion which was followed by subsequent lysis and recanalisation. Henderson *et al.*[7] using serial angiography showed recanalisation of a thrombotic occlusion which had caused myocardial infarction in a young woman who had been taking an oral contraceptive. It is possible that prostacycline-induced recanalisation may be as rapid as thromboxane-induced thrombosis in a vessel whose endothelium has been damaged by smoking and that infarction is caused by regional embolisation of the aggregates. This could account for normal coronary angiograms even when angiography is carried out within hours of infarction.[3]

Thrombosis causing myocardial infarction in the absence of significant atheromatous disease of the coronary vessels can only be postulated in patients whose subsequent coronary arteriograms are normal. It is likely that there is another and perhaps larger group of patients who have had thrombotic occlusions which have not recanalised. Recently we have recognised two such patients. Both patients were included in group 2 and were two of the five patients with myocardial infarction and an abnormal coronary arteriogram who had proximal occlusion in only one vessel. The first case was a 38-year-old hotelier who smoked 20 cigarettes a day and had a large anterior myocardial infarction. This was complicated by recurrent ventricular tachycardia from which he died four years later. Necropsy showed a full thickness anterior wall infarct with old recanalised thrombus in the proximal left anterior descending coronary artery and no significant coronary atheroma. The second case was a 34-year-old clergyman who smoked 30 cigarettes a day and had a large anterior myocardial infarct. This was complicated by recurrent refractory ventricular tachycardia from which he died four weeks later. At necropsy there was a fresh anterior wall infarct with recent thrombus in the proximal left anterior descending coronary artery and no significant coronary atheroma.

Necropsy studies of similar patients who have died after thrombotic occlusion and who have been found to have no atheromatous coronary disease have previously been described by Zacks[8] and by Eliot *et al.*[9] These cases tell us that thrombotic occlusion can cause myocardial infarction in the absence of atheroma. In such cases normal coronary arteriograms may follow recanalisation and be the tell-tale tip of the iceberg, for a thrombotic occlusion which has not recanalised cannot be distinguished with any certainty angiographically. Neither can a recanalised artery be recognised if there has been no sizeable infarct in its territory.

How then, are we to recognise such patients? Rosenblatt and Selzer[4] have emphasised a different clinical course in which myocardial infarction is usually unheralded and not preceded by angina. Subsequent angina and reinfarction is rare and prognosis should be good for it is largely dependent on the size of the infarct and possible development of arrhythmia. Only two of our group 1 patients had angina or any form of pre-infarction syndrome; one patient had angina after infarction for three months and he subsequently became asymptomatic; two patients developed breathlessness and atypical chest pain and are now asymptomatic after excision of left ventricular apical aneurysms. The patient who continued to smoke had two subsequent myocardial infarctions without angina but has been asymptomatic since giving up cigarettes three years ago. None of the remaining six patients had any form of angina after myocardial infarction and none has died during the follow-up period. In contrast, 20 per cent of the group 2 patients with myocardial infarction and an abnormal coronary arteriogram are dead, 70 per cent had preinfarction angina, and 65 per cent had postinfarction angina.

The risk factors may provide a distinguishing clinical feature. None of the patients in the myocardial infarction and normal coronary arteriogram group had raised cholesterol or hypertension, but 90 per cent were heavy cigarette smokers. In contrast, 82 per cent of the patients with myocardial infarction and an abnormal coronary arteriogram had raised cholesterol and 25 per cent were hypertensive. Seventy-five per cent of the patients in group 2 were cigarette smokers and heavy cigarette smoking was common to each group.

Epidemiological evidence suggests that cigarette smoking contributes to the development of coronary atherosclerosis.[10-12] More recently, several epidemiological studies have suggested that cigarette smoking can trigger acute coronary events in patients with underlying coronary artery disease.[13 14] The Framingham Study has shown that men who were former smokers on entry to the study had coronary heart disease rates over an 18-year follow-up period that were no higher than those of men who had never smoked. Wilhelmsson *et al.,* in Sweden,[14] have shown that young or middle-aged men who stop smoking show a major reduction in rates of coronary heart disease as compared with those who continue to smoke. Doyle[15] has written that cigarette smoking is a weak risk factor on its own, though smoking greatly increases the probability of acute coronary events in patients with hypertension or hypercholesterolaemia. Most transmural infarcts in atheromatous subjects result from final thombotic occlusion of a chronically narrowed vessel[16] and it seems that smoking might trigger this event.

Can cigarette smoking cause coronary thombosis in the absence of atheroma? This is the unproven but suggested hypothesis. The effects of inhaled smoke containing nicotine and carbon monoxide are multiple: increased catecholamine release, increased carboxyhaemoglobin, endothelial swelling, narrowing of the vessel lumen, arterial spasm, increased platelet stickiness, increased platelet aggregation, and inhibition of fibrinolysis.[17] Further information about platelet behaviour in these patients is required.

Khan and Haywood[2] reported 78 consecutive patients with myocardial infarction under the age of 50 who had selective coronary arteriograms. They found nine patients (12%) who had normal coronary arteriograms: cigarette smoking was the sole major risk factor in eight of these patients and the mean consumption per person was 30 cigarettes per day. In our institution nine of the 40 patients (25%) under the age of 40 with myocardial infarction who were investigated by selective coronary arteriography had normal coronary arteriograms; in these nine patients mean cigarette consumption was 25 per day. These are the two largest reported series of myocardial infarction with normal coronary arteriogram and in both series smoking was the sole major risk factor. It is essential to recognise this group of patients with normal coronary arteriograms because it includes a significant proportion of young patients with myocardial infarction and because there are important therapeutic implications. In suffering myocardial infarction at a young age these patients have identified themselves as being at particular risk; if cigarette smoking was the trigger, it is important that they stop. Eight of our 10 patients did so and had no recurrence of myocardial infarction, angina, or other coronary events. One patient continued to smoke 60 cigarettes per day and had two further myocardial infarctions.

In our study five of the 30 patients who had myocardial infarction and an abnormal coronary arteriogram had a proximal occlusion in only one vessel. In two of these patients there was no significant atheroma at necropsy. Angiographically it may be impossible to differentiate thrombotic occlusion from atherosclerotic occlusion, but the clinical presentation and risk factor profile in patients with non-atheromatous occlusive coronary disease is distinctive and recognisable.

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Br Heart J 1980; **43:** 499–505

Nuclear angiography in convalescent phase of myocardial infarction

Serial study of left ventricular performance

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SUMMARY Electrocardiograph-gated blood pool scans (anteroposterior and left anterior oblique projections) were recorded in 30 patients seven to 10 days after myocardial infarction. Left ventricular ejection fractions (mean 0·26±0·10) were lower on average than values previously obtained in 11 normal subjects (mean 0·52±0·06) and correlated broadly with the clinical assessment of left ventricular performance. Ejection fractions were lower in anterior (mean 0·21±0·09) than inferior (mean 0·32±0·08) infarcts. Abnormal wall motion was detected in 11 of 15 anterior infarcts and in six of 13 inferior infarcts: mean ejection fractions associated with global asynergy, segmental asynergy, and normal wall motion were 0·15, 0·26, and 0·36, respectively.

Twenty-four patients were reinvestigated two months later. Though there was some change in the clinical status of eight patients, wall motion and ejection fraction were unchanged (mean difference -0·005±0·036).

Twelve patients were reinvestigated six months after infarction. The ejection fraction for the group was significantly lower than the values obtained at 10 days and two months, and four individual changes were significant when compared with the first study. Changes in wall motion were observed in one patient.

From this radionuclide study, we conclude that ejection fraction and wall motion do not improve after the early convalescent phase of myocardial infarction.

Nuclear angiography is now widely used for the assessment of left ventricular performance.[1–3] This paper presents the results of a serial radionuclide study of left ventricular ejection fraction and wall motion in patients convalescing from myocardial infarction.

Patients

STUDY 1

Thirty patients aged 35 to 78 (mean 56) years were investigated seven to 10 days after acute myocardial infarction, that is just before discharge from hospital. All had raised cardiac enzymes: 27 had Q wave and ST-T changes of acute myocardial infarction and three had ST-T changes only. On electrocardiographic evidence, the site of acute infarction was anterior in 15 patients, inferior in 13, anterior and inferior in one, and true posterior in one: two patients had a history and electrocardiographic evidence of previous myocardial infarction. All patients were in sinus rhythm and all but three were normotensive.

Left ventricular performance was assessed clinically and radiographically and the patients were grouped as follows. In 14 patients, left ventricular failure was judged to have been absent at all times (group 1). In six patients, signs of failure were present soon after infarction but had resolved by the time of study (group 2). In 10 patients, signs of failure persisted at the time of study despite a full anti-failure regimen (group 3). All patients in groups 2 and 3 were on diuretics and eight were

Received for publication 10 August 1979

also on digoxin. Three group 1 patients were on beta-adrenergic blocking agents.

STUDY 2

Twenty-four patients were reinvestigated approximately two months after myocardial infarction. On clinical and radiographic evidence, four patients had deteriorated and four had improved since study 1; the clinical status of the remaining 16 patients was judged to be unchanged.

STUDY 3

Twelve patients were investigated for a third time approximately six months after myocardial infarction. On clinical and radiographic evidence, two patients had deteriorated since study 2; the clinical status of the remaining 10 patients was judged to be unchanged.

Methods

The patients were investigated at rest. After the intravenous injection of 20 mCi of 99^{m}-technetium-labelled human serum albumin, patients lay under a gamma camera* positioned to achieve optimum separation of the left and right ventricles in the left anterior oblique projection (typically 30° with 10° caudal tilt). Acquisition and analysis were carried out on a micro-computer.† The heart rate was determined automatically and the electrocardiograph signal was used to trigger 16 sequential images of the cardiac cycle. Acquisition was suspended if intervals outside ±20 per cent of the initial RR interval estimate were detected. Each image was acquired in a 64 × 64 data matrix and acquisition was terminated automatically when a preset count density of 200 counts/pixel over the left ventricle had been achieved in the end-diastole image. The 16 images were then stored on magnetic tape for later analysis. This procedure was repeated to acquire images in the anteroposterior view.

Images underwent nine-point smoothing, and were displayed in a continuous cinematic mode. For background estimation, a light pen was used to define an area adjacent to the apex of the left ventricle in the left anterior oblique view. The count density in this area during the cardiac cycle was displayed. If this was reduced at end-systole, a new area further removed from the left ventricle was selected. The average background count density in the selected area was then subtracted from each frame. Background corrected images were displayed cinematically and the end-diastolic outline was defined by automatically selecting up to 16 points with the light pen. The area of interest of the left ventricle was defined by joining these points. Total counts within this region were calculated for each image and the average time-activity curve for the left ventricle during the cardiac cycle was displayed. Ejection fraction (EF) was calculated from the maximum and minimum counts in the region of the left ventricle using the following equation:

$$\mathrm{EF} = \frac{\mathrm{C\,max} - \mathrm{C\,min}}{\mathrm{C\,max}}$$

where, C max = background corrected counts at end-diastole, and C min = background corrected counts at end-systole.

We have previously measured the precision of the method by assessment of the same data by two observers. The standard deviation for a single measurement of ejection fraction was found to be 0·024, and for differences in pairs of measurements 0·035. Therefore, the difference in two estimates required to achieve 95 per cent probability is 0·07

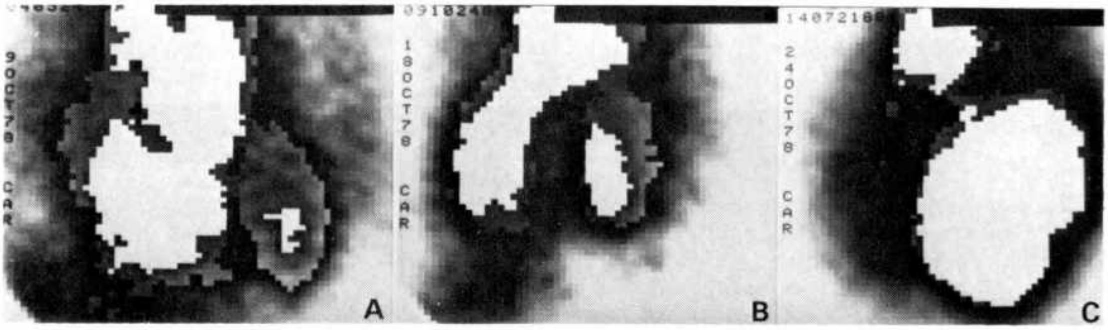

Fig. 1 *Three categories of wall motion (see text) are illustrated:* (A) *no asynergy,* (B) *segmental asynergy,* (C) *global asynergy. LAO projection: end-systolic and end-diastolic images have been superimposed.*

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* Ohio-Nuclear 410. † Ohio-Nuclear VIP 450.

and we have used this as our criterion for determining the significance of changes in ejection fraction.

The smoothed background corrected images were displayed cinematically and a line of equal count density (contour) was used to investigate the wall motion of the left ventricle in the anteroposterior and left anterior oblique views. This contour was adjusted by the operator until the left ventricular shape was visualised. The contour lines at end-diastole and end-systole were superimposed and recorded photographically. The relative wall motion was inferred from the degree of contour contraction in different directions from the centre (Fig. 1) and was classified as follows:

No asynergy: symmetrical contraction of the contours in all directions.

Segmental asynergy: reduced contraction of the contours in a particular direction.

Global asynergy: negligible contraction of the contours in all directions.

Results

STUDY 1

Left ventricular ejection fraction

Ejection fractions ranged from 0·09 to 0·45 (mean 0·26 ±0·10)* and were lower on average than values previously obtained in 11 normal subjects (0·42 to 0·62: mean 0·52 ±0·06).

Ejection fractions associated with anterior infarcts (mean 0·21 ±0·09) were significantly lower ($p < 0{\cdot}01$) than ejection fractions associated with inferior infarcts (mean 0·32 ±0·08).

In that the lowest ejection fractions were recorded in patients with persisting left ventricular failure (group 3) and the highest were recorded in patients without evidence of failure (group 1), the ejection fraction correlated broadly with the clinical assessment of left ventricular performance (Fig. 2). There was, however, some overlap between categories and only groups 1 and 3 differed significantly ($p < 0{\cdot}01$).

Table *Relation between wall motion and electrocardiographic site of infarction in study 1*

Wall motion category	*Infarct site (electrocardiogram)*			
	Anterior	*Inferior*	*Anterior/ inferior*	*True posterior*
No asynergy	4	7	1	1
Segmental asynergy	4	4	0	0
Global asynergy	7	2	0	0

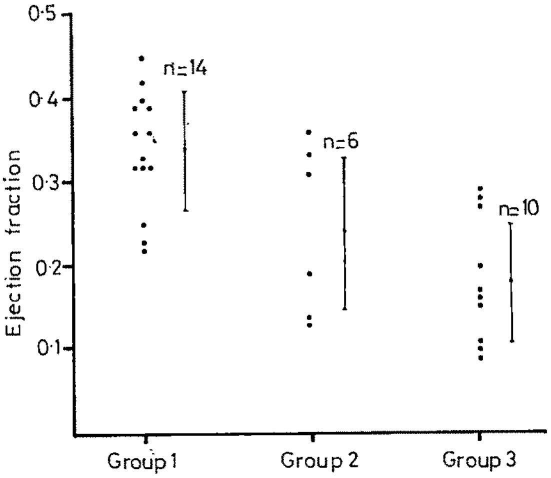

Fig. 2 *Left ventricular ejection fraction in three clinical groups (see text). Mean values and standard deviations for groups 1, 2, and 3 are 0·34±0·07, 0·24±0·09, and 0·18±0·07, respectively.*

Wall motion

In 13 patients there was no evidence of ventricular asynergy (Fig. 1A): segmental asynergy (Fig. 1B) was detected in eight patients and global asynergy (Fig. 1C) in nine. The Table shows the relation between wall motion and electrocardiographic site of infarction. In the eight patients with segmental asynergy, the electrocardiographic site of infarction correlated with the wall motion abnormality in six instances.

In that the lowest ejection fractions were recorded in patients with global asynergy and the highest ejection fractions were recorded in patients without asynergy, wall motion correlated broadly with ejection fraction (Fig. 3).

STUDY 2

Left ventricular ejection fraction

Ejection fractions ranged from 0·08 to 0·55 (mean 0·28 ±0·11). Values for the group were not significantly different (paired t test) from those obtained in study 1 (mean difference = −0·005 ±0·036) and only one significant individual change (+0·10) was observed.

In 15 patients, both ejection fraction and clinical status were unchanged. In eight patients ejection fraction was unaltered but clinical status was judged to have changed. In one patient ejection fraction changed significantly but the clinical status was unchanged.

Wall motion

No changes were observed.

STUDY 3

Left ventricular ejection fraction

Ejection fractions (Fig. 4) ranged from 0·15 to 0·40

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* All error values quoted are standard deviations.

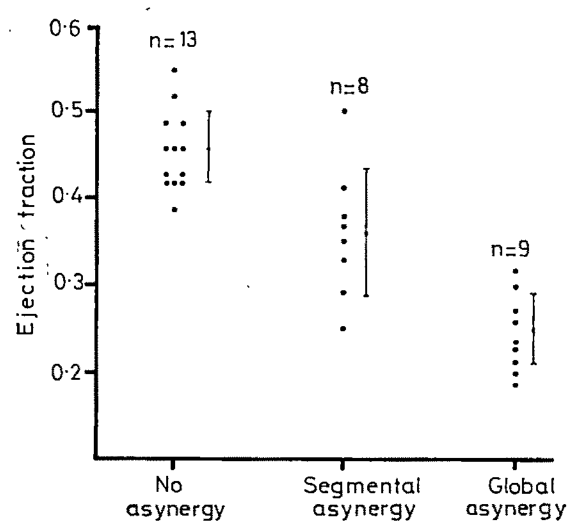


Fig. 3 *Relation between left ventricular ejection fraction and wall motion. Mean values and standard deviations for no asynergy, segmental asynergy, and global asynergy are 0·36±0·04, 0·26±0·07, and 0·15±0·04, respectively.*

(mean 0·27 ±0·07). Values for the group were significantly ($p < 0{\cdot}01$, paired t test) different from values obtained in study 2 (mean difference = −0·031 ±0·026) but no individual change was significant. Thus, the clinical deterioration which had occurred in two patients was unaccompanied by a significant change in ejection fraction.

Values for the group were significantly ($p < 0{\cdot}001$, paired t test) different from values obtained in study 1 (mean difference = −0·045 ±0·030) and the ejection fraction fell significantly in four patients. There was an accompanying change in clinical status in only one of these; patient AH (Fig. 4) had unstable angina at study 3.

Wall motion

Only one change was observed; patient AH (Fig. 4) had no evidence of ventricular asynergy at studies 1 and 2 but segmental asynergy was observed at study 3 (Fig. 5).

Discussion

There is ample evidence that the radionuclide ejection fraction can be measured reproducibly and that it is valid to use it in the serial assessment of left ventricular performance.[3–5] Radionuclide ejection fractions have generally been found to be lower than values obtained by contrast angiography.[3 4] The values obtained here in normal subjects agree well with those reported by others.[6 7]

In the early convalescent phase (study 1) only two patients, one with electrocardiographic evidence of both fresh anterior and fresh inferior myocardial infarction, had ejection fractions within our normal range. The high incidence of abnormal ejection fractions in this phase and the broad correlation between ejection fraction and clinical assessment (Fig. 2) are in line with the findings of a previous nuclear angiographic study.[8] The clinical status of most of our patients was unchanged over the months after infarction and in these instances the unaltered ejection fraction was in order. However, the discrepancies between ejection fraction and clinical assessment in studies 2 and 3 raise questions about the sensitivity of the radionuclide technique, the value of the resting ejection fraction as a measure of left ventricular performance, and the accuracy of our clinical judgment.

Ejection fraction as measured by nuclear angiography does not improve from the tenth day to the sixth month after myocardial infarction. Further, it appears on present evidence that ejection fraction tends to deteriorate over this period. There are obvious therapeutic implications which may merit further investigation. Thus, for example, the withdrawal of diuretic treatment in late convalescence from a patient shown to need it in the early convalescent phase seems to be inadvisable.

Schelbert *et al.*[8] reported that the radionuclide ejection fraction improves between the early and late convalescent phases of myocardial infarction. Their baseline studies were performed within five days of infarction and thus possibly before their patients had achieved cardiovascular stability: this may explain the difference between their findings

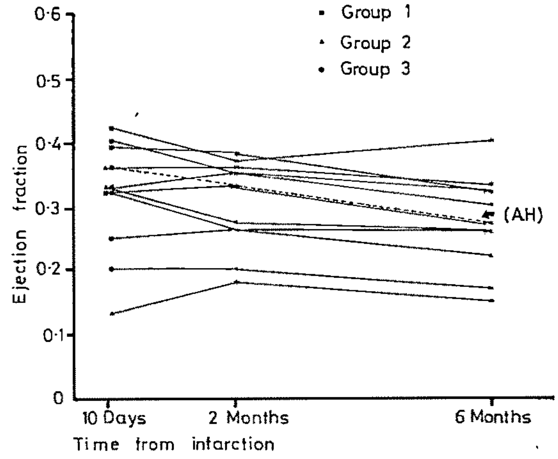


Fig. 4 *Serial measurements of left ventricular ejection fraction in 12 patients.*

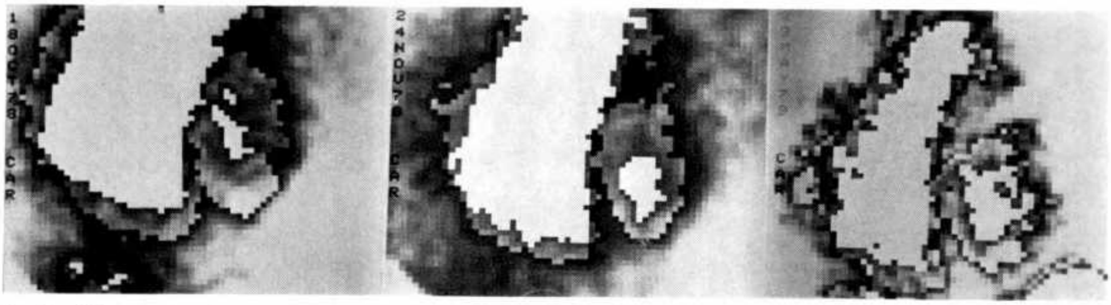


Fig. 5 *Wall motion (LAO projection) in the same patient (AH) 10 days, two months, and six months after infarction: end-systolic and end-diastolic images are superimposed.*

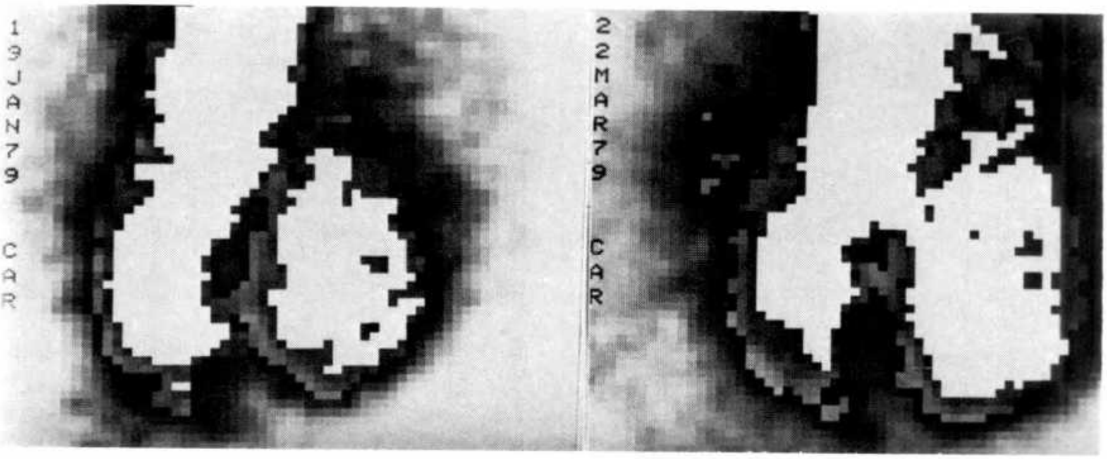
and ours. The present results are in line with the observations of Kupper *et al.*[9]: they found almost no change in pulmonary artery end-diastolic pressure and cardiac index between the sixth week and tenth month after infarction.

Doubts have been expressed about the validity of radionuclide studies of wall motion.[10] However, we were able to define three broad categories of wall motion, and believe that the isocount contour method can provide useful information on relative wall motion. The consistency of the method is illustrated in Fig. 6B, which was produced two months after Fig. 6A and without reference to it by an observer who had no knowledge of the infarct site or of the patient's clinical status.

The preponderance of wall motion abnormalities in patients with anterior infarcts (Table) could simply reflect inadequate imaging of the left ventricular inferior wall in the anteroposterior and left anterior oblique projections. However, the fact that the ejection fraction was lower in anterior than in inferior infarcts suggests that the difference in the incidence of wall motion abnormalities is real.

The correlation between left ventricular ejection fraction and wall motion (Fig. 3) is to be expected and has been reported previously.[8 11] The patient in whom a change in wall motion was observed (Fig. 5) was one of four patients in whom ejection fraction fell significantly between the tenth day and the sixth month after infarction (Fig. 4).

Nuclear angiography provided information which was of some value in the practical management of this particular group of patients. Thus, one myocardial aneurysm was detected (Fig. 7), the



A B

Fig. 6 *Wall motion (LAO projection) in the same patient with an interval of two months between studies: end-systolic and end-diastolic images are superimposed.*

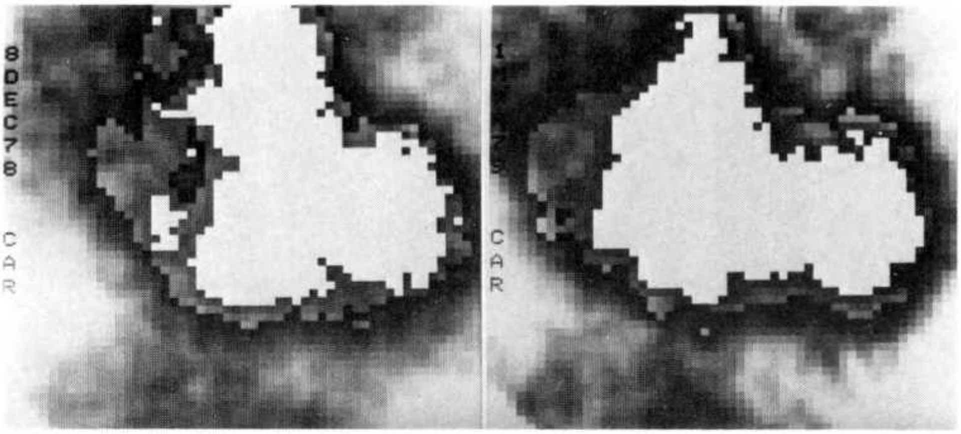


Fig. 7 *Wall motion (AP projection) with an interval of three months between studies. Appearances suggest the development of an apical aneurysm.*

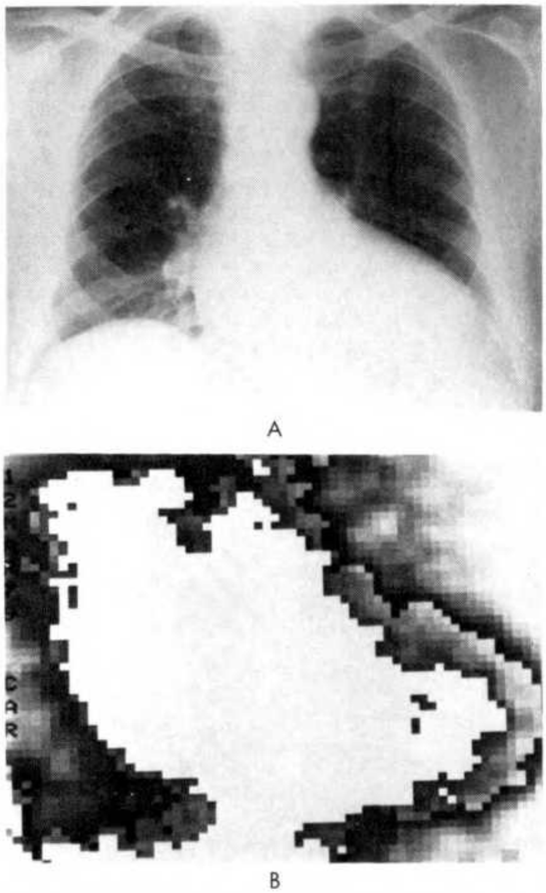


Fig. 8 (A) *Chest* x-*ray*. (B) *Wall motion in AP projection from a patient with possible right ventricular infarction (see text).*

possiblity of excising an infarcted segment was ruled out in the patients with global asynergy, and one patient with possible right ventricular infarction was identified (Fig. 8). This patient had an inferior infarct, a raised jugular venous pressure, cardiomegaly, and resistant supraventricular and ventricular arrhythmias. Despite these features, left ventricular ejection fraction was above average for the group, and there was no evidence of ventricular asynergy (Fig. 8B). The radionuclide images indicated that the radiographic appearances (Fig 8A) could be accounted for by right ventricular enlargement.

Nuclear angiography defines the extent to which left ventricular performance has been impaired by a myocardial infarction, and there seems to be a place for it in the routine assessment of infarct patients. As we have shown that the findings are unlikely to change during later convalescence, a single nuclear angiographic assessment, which can be undertaken before discharge from hospital, should be adequate. While serial studies of wall motion and ejection fraction may be indicated in some patients, for example those with suspected myocardial aneurysm formation, their value in the routine follow-up of infarct patients is doubtful.

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Br Heart J 1980; **43**: 506–13

Left ventricular systolic time intervals in patients with acute myocardial infarction

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SUMMARY Left ventricular systolic time intervals were measured daily during 601 episodes of acute myocardial infarction. The ratio of pre-ejection period to ejection period during the first 24 hours permitted patients to be arranged in six prognostic groups with mortalities while in hospital ranging from 4 to 60 per cent. The only factors completely independent of the systolic time intervals which were shown statistically to be associated with high mortality while in hospital were defects in atrioventricular and intraventricular conduction.

Various prognostic scoring schemes have been devised for patients who have sustained an acute myocardial infarction. Those of Peel and co-workers,[1] of Killip and Kimball,[2] and of Norris and co-workers[3] are still widely used. Items of information which have been derived both subjectively and objectively are often incorporated in such scores. In terms of morbidity and mortality, however, the short-term prognosis is determined almost solely by the extent of the damaged myocardium.[4–11] The damaged tissue may contain areas of necrosis, both old and new, plus areas of muscle which, though still viable, contract feebly. Hori and co-workers[12] showed that the total volume of injured tissue was inversely related to certain measures of the pumping effectiveness of the heart. Indeed, a reliable prognostic score may be derived solely from appropriate measurements of the pumping effectiveness of the heart.[13–21] Ideally, such measurements should be obtainable non-invasively. Systolic time intervals provide a convenient non-invasive method for assessing left ventricular pumping effectiveness.[22] As would be expected, therefore, the short-term prognosis of patients with acute myocardial infarction correlates with their systolic time intervals.[23–33] Reservations have been expressed, however, concerning the accuracy of the systolic time intervals in measuring the pumping effectiveness of the heart in patients with acute myocardial infarction, and hence of their prognostic significance.[34–40] The present study is an attempt to refine the techniques of recording and measuring systolic time intervals so that a more reliable prognosis can be made in patients with acute myocardial infarction, particularly in relation to their mortality while in hospital.

Received for publication 12 November 1979

Subjects and methods

Patients admitted to the Leicester Royal Infirmary who fulfilled the World Health Organization criteria[41] for a "definite acute myocardial infarction" were studied prospectively. A total of 601 distinct episodes of acute myocardial infarction during 596 separate admissions in 578 persons form the basis of this report. The majority of these people had sought attention in a public accident department on account of retrosternal discomfort, which was still present in 86 per cent on arrival at the hospital. The author visited the wards at least once and usually twice each day to examine every patient suspected on clinical grounds of having an acute myocardial infarction. Inevitably, a few patients were accidentally overlooked and a few died so soon after admission that electrocardiographic and biochemical evidence needed to secure the diagnosis was not obtained. A few patients with a proven acute myocardial infarction died before being seen by the author. The total of all these exclusions is estimated to constitute approximately 2 per cent of the total of acute myocardial infarctions in patients who were alive on arrival at the hospital during the period of this study. A standard 12 lead electrocardiogram was recorded on admission and routinely on a daily basis for the first few days in hospital and whenever a change of cardiac rhythm was noted by the ward staff. Patients were connected to bedside electrocardiograph oscilloscope monitors for approximately the first three days in hospital. All disturbances of cardiac rhythm recorded electrocardiographically were classified by the author using the criteria of Schamroth.[42] Venous blood was analysed for creatine kinase, aspartate aminotransferase, and hydroxybutyrate dehydrogenase on a daily basis for approximately the first three days in hospital. Serum concentrations of creatine kinase and at least one of the other two enzymes were required to be above the upper limit of the locally defined normal range in at least one blood sample to qualify for the World Health Organization description[41] of "elevated serum enzymes". Rises in serum creatine kinase were not accepted as evidence of acute myocardial infarction in patients with clinical evidence of recent injury to brain or skeletal muscle, or who had received electrical cardioversion, or who had convulsed in the preceding four days, or who were myxoedematous by biochemical criteria.

Most patients received an oxygen enriched atmosphere to breathe for the first 24 hours. This was delivered via plastic nasal prongs. Initial pain relief was provided with diamorphine administered parenterally. Nausea was relieved as far as possible with the aid of prochlorperazine administered parenterally. Left ventricular failure was treated initially and mainly with frusemide given intravenously, followed later, if required, by frusemide or a thiazide diuretic given orally. Few received digoxin for this purpose. Heparin was administered subcutaneously and prophylactically to an increasing proportion of the patients as the period of this study continued. Antiarrhythmic drugs were not administered routinely on a prophylactic basis. Ventricular extrasystolic activity of sufficient severity to cause concern to the ward staff was usually treated with lignocaine, 2 or 3 mg/min, intravenously. In the few patients where this was ineffective, alternative agents such as mexiletine or disopyramide were used. Digoxin was administered orally to patients with atrial fibrillation. Few patients received beta-receptor blocking agents while in hospital, and these were mainly persons who had received them previously for angina or arterial hypertension. Pericarditic pain was usually treated with a short course of indomethacin given orally. Other complications and concomitant diseases occurred so infrequently or were managed in so many different ways that it is not possible to make generalisations about treatment.

The majority of patients were nursed on acute medical wards, but a few were managed for all or part of their time on other wards including one with facilities for positive pressure ventilation. During the period of this study no specially designated coronary care unit existed in the hospital. Because of various degrees of atrioventricular block and the expected need for electrical pacing, or because of a need for cardiac catheterisation, 15 patients were transferred to other hospitals. The fate of these patients after transfer is included in this report. Patients were deemed to have survived if they were discharged to their own home or to a local convalescent home. The overall survival rate was 84 per cent and the average duration of hospital stay of survivors was 13 days. The non-survivors lived for an average of three days from onset of symptoms.

RECORDING OF SYSTOLIC TIME INTERVALS

As soon as possible after admission of the patient to the ward (referred to as day 1), left ventricular systolic time intervals were measured by the author from a simultaneous recording of an electrocardiogram, a phonocardiogram, and a carotid pulse trace, recorded strictly according to the recommendations of Weissler.[22] The median time interval between the onset of persistent chest discomfort and the first recording of systolic time interval was 12 hours, approximately four hours of which was the result of delay in getting to hospital and a further three hours in getting to the ward. All traces were made at a paper speed of 100 mm/s on an ultraviolet recorder of type M19UV made by Devices of Welwyn Garden City, Hertfordshire. An electrocardiographic lead showing a Q wave was selected. The phonocardiogram was recorded in most patients from the third intercostal space at the left sternal edge, using a microphone of type MSC-IT, made by Nihonkohden of Tokyo, Japan, which was attached to the chest wall with a rubber strap. The output from the microphone was led to an amplifier of type 3545 made by Devices and adjusted to respond maximally in the range 6 to 10×10^2 Hz, with attenuation below this range. The amplifier was adjusted to delineate clearly the aortic (first) component of the second heart sound (A2). The recording position and frequency responsive range sometimes needed to be modified slightly in patients with a systolic murmur or rub. The carotid pulse trace was recorded by placing a hand-held hollow hemispherical plastic cup (diameter 2 cm) against the side of the neck directly over the right common carotid artery, just medial to the sternocleidomastoid muscle. In a few patients with absent right carotid pulsation the recording was made from the left side. The cup was connected via a 6 cm length of air-filled thick-walled plastic tubing (internal diameter 4 mm) to a pressure transducer of type 4-327-L221, made by Bell & Howell of Basingstoke, Hampshire. The output from the transducer was led via an amplifier of type 3552 to another of type 3551 (both made by Devices) adjusted to give an undamped response below 30 Hz. The time constant of the whole assembly was in excess of five seconds, and there was no frequency-dependent phase shift detectable below 10^2 Hz. The carotid pulse trace was adjusted to approximately 12 cm amplitude in all patients, including those with feeble pulses. All recordings were obtained with the patients' legs supported horizontally on a bed and with the head and upper trunk at approximately 45° to the horizontal. Recordings were made once each day, with the patient breathing spontaneously.

CALCULATION OF SYSTOLIC TIME INTERVAL
Left ventricular systole begins with the Q wave of the electrocardiogram and ends with the A2 sound (the QA2 interval). The left ventricular ejection period (EP) was the time from the beginning of the upstroke of the carotid pulse trace to its incisura. The pre-ejection period (PEP) was calculated as follows:

$$\text{PEP} = \text{QA2} - \text{EP}$$

Unlike the PEP and the EP separately, the ratio PEP/EP is independent of heart rate.[22]

At least 20 consecutive heart beats were averaged to obtain a representative value of PEP/EP in patients with atrial fibrillation. A mean of at least 10 heart beats (as far as possible consecutive beats uninterrupted by extrasystoles or dropped beats) during two to four complete respiratory cycles was measured in other patients. Any recorded extrasystoles were ignored when calculating systolic time intervals, as were heart beats immediately after extrasytoles, on account of post-extrasystolic potentiation. Patients with QRS complexes showing a left bundle-branch block pattern have a large and variable prolongation of the pre-ejection period. In addition, the first component of their second heart sound does not coincide with aortic valve closure. In this study, therefore, patients with this abnormality did not have systolic time intervals measured. In a few patients with a stable ectopic pacemaker apparently in the left ventricle the systolic time intervals were measured in the usual way. There were no patients with a stable ectopic pacemaker apparently located in the right ventricle on admission, though this developed while in hospital in one patient, at which time systolic time interval measurements were discontinued.

Results

Preliminary studies showed that the mean value of PEP/EP among 170 patients of both sexes in hospital who were between 30 and 70 years and were without evidence of any cardiovascular disease was 0·28 ±SE 0·03. Patients with acute myocardial infarction who displayed unequivocal evidence of left ventricular failure as judged by physical examination (classes 3 and 4 of Killip and Kimball[2]) almost invariably (98%) showed a value of PEP/EP in excess of 0·33. Most of these patients showed both an abnormally prolonged pre-ejection period and an abnormally shortened ejection period as judged from the heart rate-adjusted values quoted by Weissler.[22] In a minority (16%) of this group, however, the high value of PEP/EP was the result of an isolated abnormality in either the numerator or the denominator. The PEP/EP ratio seems to be more reliable than either of its components, therefore, in detecting moderate and severe left ventricular failure. For this reason the ratio was adopted as the routine measure of left ventricular pumping effectiveness in the present study.

The PEP/EP ratio showed a characteristic rise and subsequent fall in most patients during the first few days after the onset of acute myocardial infarction (Fig.). The extent of the rise in PEP/EP and its timing showed little correlation with survival. In contrast, the magnitude of the first recorded value of PEP/EP was closely correlated with the subsequent mortality in hospital. For the remainder of this report, therefore, patients are arranged in six prognostic groups depending upon their PEP/EP value on day 1 (Table 1). Groups 1 and 2 combined contained 64 per cent of the

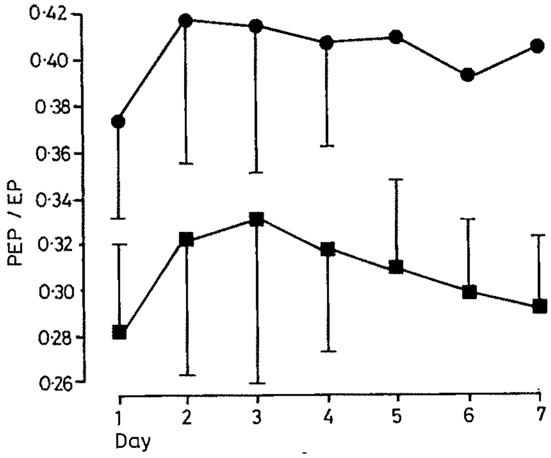

Fig. *Daily mean PEP/EP values in survivors* (squares) *and in eventual non-survivors* (circles). *Vertical bars represent SD of mean. There were 476 eventual survivors and 86 eventual non-survivors on day 1. The number of eventual non-survivors declined thereafter. By day 5 there were too few eventual non-survivors to permit a meaningful calculation of SD of mean.*

Table 1. *Numbers of patients showing various features, arranged according to PEP/EP value on day 1*

	Group 1 PEP/EP < 0·30	*Group 2 PEP/EP 0·30–0·33*	*Group 3 PEP/EP 0·34–0·37*	*Group 4 PEP/EP 0·38–0·41*	*Group 5 PEP/EP > 0·41*	*Group 6 LBBB*
Patients in group	251	131	66	49	65	39
Non-survivors in group	10 (4)	10 (8)	11 (17)	16 (33)	39 (60)	12 (31)
Patients with diabetes mellitus	24	10	13	12	8	5
Non-survivors with diabetes mellitus	0 (0)	0 (0)	3 (23)	4 (33)	5 (63)	1 (20)
Patients with old myocardial infarction	38	29	17	11	22	15
Non-survivors with old myocardial infarction	0 (0)	2 (7)	2 (12)	7 (64)	17 (77)	5 (33)
Female patients	30	16	8	5	17	6
Female non-survivors	3 (10)	2 (13)	2 (25)	2 (40)	14 (82)	1 (17)
Patients with atrial fibrillation	32	28	7	12	18	8
Non-survivors with atrial fibrillation	5 (16)	4 (14)	2 (29)	5 (42)	12 (67)	5 (63)
Patients with right bundle-branch block	12	14	3	7	12	0
Non-survivors with right bundle-branch block	3 (25)	3 (21)	1 (33)	6 (86)	9 (75)	0 (0)
Patients with third degree atrioventricular block	8	8	6	4	5	1
Non-survivors with third degree atrioventricular block	4 (50)	3 (38)	4 (67)	2 (50)	4 (80)	0 (0)
Mean age of patients	58 years	61 years	65 years	63 years	64 years	71 years
Mean age of non-survivors	68 years	69 years	59 years	65 years	66 years	73 years

Figures in parentheses represent the non-survivors as a percentage of the patients showing a particular feature within the group.

patients and showed a mortality of only 5 per cent. Groups 3 to 5 contained fewer patients but a progressively higher mortality (χ^2 test, $p < 0{\cdot}00001$). Group 6 consisted of patients with left bundle-branch block on admission, who also showed a substantial mortality while in hospital.

In 11 per cent of patients with acute myocardial infarction, despite having no clinical evidence of cardiac failure (belonging to class 1 of Killip and Kimball[2]), the PEP/EP value on day 1 was greater than 0·33. The mortality of these patients while in hospital was 14 per cent, which is approximately treble that of patients with a PEP/EP value on day 1 of 0·33 or less. Some, but not all, of these patients with apparently subclinical cardiac failure had received narcotic analgesic or diuretic drugs before the measurement of the systolic time interval, which may account in part for their lack of physical signs. Basal lung crepitations (cardiac failure class 2 of Killip and Kimball)[2], on the other hand, were heard by the author on day 1 in 21 per cent of patients when the PEP/EP recorded at the same time was less than 0·30. Such patients showed a mortality in hospital which was no greater than that of patients with a complete absence of evidence of cardiac failure. These observations suggest that the classical clinical signs of mild left ventricular failure are less successful than systolic time intervals in assessing the prognosis of these patients.

Previous workers have noted a statistical association between the mortality of patients with acute myocardial infarction and certain features such as their age and sex or the coexistence of other morbid conditions such as diabetes mellitus or a previous myocardial infarction. Abnormalities of cardiac rhythm such as atrial fibrillation, right bundle-branch block, or third degree atrioventricular block also have been reported to be associated with poor short-term survival.[1] The frequency with which these features were noted in groups 1 to 6 together with the associated mortalities is shown in Table 1.

The members of group 6 were significantly older than the other patients in the study, and the survivors in group 1 were significantly younger than the other patients (in both cases $p < 0{\cdot}01$, using Student's t test). There was no statistically significant difference between the ages of the other groups of patients or between the ages of the other survivors and non-survivors. Thus, age had only a small impact upon short-term survival in the present study.

Sufficient numbers of patients to permit a useful statistical analysis by means of the χ^2 test were obtainable only by combining some of the groups. Thus, Tables 2 and 3 have been constructed with groups 1 and 2 combined on the one hand, and with groups 3 to 6 combined on the other hand. Table 2 shows that diabetes mellitus, myocardial infarction, right bundle-branch block, and third degree atrioventricular block were more frequent among groups 3 to 6 than among groups 1 and 2. Except in the case of the female sex and third degree atrioventricular block these differences reached an acceptable level of statistical significance. Table 3 shows the impact of these features upon short-term mortality. In contrast to the findings of some previous investigators the presence or absence of diabetes mellitus was associated with no significant difference in mortality. In contrast, a previous myocardial infarction or female sex were both associated with a greater mortality than where these features were absent. The difference in

Table 2 *Percentage prevalence of various features among patients arranged according to the PEP/EP value on day 1*

	All groups combined	*Groups 1 and 2 combined (PEP/EP < 0·34)*	*Groups 3 to 6 combined (PEP/EP > 0·33 plus LBBB)*	*p**
Patients with diabetes mellitus	12	9	17	0·0060
Patients with old myocardial infarction	22	18	30	0·0013
Female patients	14	12	16	0·1505
Patients with atrial fibrillation	18	16	25	0·0061
Patients with right bundle-branch block	8	7	13	0·0100
Patients with third degree atrio-ventricular block	5	4	7	0·1556

* p represents the probability, assessed by the χ^2 test, that the difference in prevalence of the listed feature between members of groups 1 and 2 combined and members of groups 3, 4, 5, and 6 combined could have occurred by chance.

mortality was statistically significant among members of groups 3 to 6 combined but not among members of groups 1 and 2 combined. In the case of atrial fibrillation the position was reversed, with a significantly higher mortality among the fibrillating as opposed to the non-fibrillating members of groups 1 and 2 combined, but not among the members of groups 3 to 6 combined. Patients showing right bundle-branch block or third degree atrioventricular block showed a distinct and consistently higher mortality than was found among those in whom these features were absent. The differences in mortality were statistically highly significant not only for members of groups 1 and 2 combined but also for the members of the other groups combined. Both right bundle-branch block and third degree atrioventricular block constitute, therefore, mortality risk factors which are fully independent of the pumping effectiveness of the left ventricle.

Too few patients with third degree atrioventricular block were provided with transvenous right ventricular electrical pacing to permit any conclusions regarding the effectiveness of this treatment in preventing death. Thus, nine patients were paced, of whom five died, whereas there were 12 deaths among the 23 non-paced patients. While in hospital, left bundle-branch block developed in 14 patients, of whom four died. This is a similarly high mortality to that shown by patients with left bundle-branch block on admission (group 6), and it is significantly higher than the overall mortality of patients in this study. Members of groups 3, 4, and 5 combined developed left bundle-branch block while in hospital significantly more frequently than the combined members of groups 1 and 2. This is consistent with the previous observations of Biddle and co-workers.[43]

Table 3 *Mortality percentages among patients grouped according to the PEP/EP value on day 1*

	Groups 1 and 2 combined	*p**	*Groups 3 to 6 combined*	*p**	*All groups combined*	*p**
Patients with diabetes mellitus	0	0·2993	35	0·8856	18	0·7523
Patients without diabetes mellitus	6		36		16	
Patients with old myocardial infarction	3	0·5179	48	0·0213	25	0·0040
Patients without old myocardial infarction	6		30		14	
Female patients	11	0·1296	53	0·0289	30	0·0009
Male patients	5		32		14	
Patients with atrial fibrillation	15	0·0006	46	0·1037	30	< 0·0001
Patients without atrial fibrillation	3		32		13	
Patients with right bundle-branch block	24	< 0·0001	62	0·0026	44	< 0·0001
Patients without right bundle-branch block	4		31		14	
Patients with third degree atrioventricular block	44	< 0·0001	69	0·0088	56	< 0·0001
Patients without third degree atrioventricular block	4		33		14	

* p represents the probability, assessed by the χ^2 test, that the difference in mortality between patients with and without the listed feature could have occurred by chance.

Discussion

The present study indicates that the short-term survival of patients in hospital with acute myocardial infarction may be predicted with considerable accuracy solely from a knowledge of the pumping effectiveness of the left ventricle as judged by the PEP/EP ratio measured on the first day. In general, this confirms the findings of previous workers (see introduction). Weissler[22] has pointed out, however, that systolic time interval measurements depend to some extent upon the value of cardiac preload and afterload, both of which represent largely uncontrolled variables in patients with acute myocardial infarction. This source of variability has been invoked as an explanation by several previous workers who failed to obtain acceptable prognostic accuracy from systolic time interval measurements (see introduction). In the present study, however, the prognostic accuracy attained was similar to that derived from measurements of cardiac pumping effectiveness based upon cardiac catheterisation, a technique which permits an allowance to be made for the prevailing conditions of cardiac preload and afterload.[21] Alternative explanations for the limited success of previous attempts at a prognosis based upon systolic time intervals are worthy, therefore, of consideration. In the author's opinion the most important factor in reliable systolic time interval measurement is strict adherence to the recommendations of Weissler.[22] The scanty details of recording and measuring technique in some previous reports of systolic time intervals in patients with acute myocardial infarction suggest that the importance of these aspects of methodology has not been appreciated by some investigators. Subsidiary and probably minor reasons for the greater prognostic success obtained in the present study compared with previous attempts may be the greater number of patients in the present work plus the fact that all recordings and measurements were performed by one operator. The usefulness of systolic time intervals in routine clinical practice, therefore, may be limited by the need to standardise so carefully the recording and measuring techniques. A large and uncontrollable variable in the present study was the variety of treatment which the patients received before and during hospitalisation. This may represent a limitation to greater prognostic precision. Efforts were made in the present study to analyse possible statistical associations between the treatment received by patients and subsequent events in hospital, both in terms of survival and in terms of systolic time interval values. Unfortunately, nothing of statistical significance emerged despite the fact that previous workers have demonstrated profound effects of these drugs on systolic time interval values. This failure is probably accounted for in part by the varied doses and times of administration of the drugs in relation to the measurements of systolic time intervals in the present study. It should be noted in this connection that the only value of PEP/EP which had prognostic significance was the first measurement. This measurement was made at an early stage, when most of the patients had already received diamorphine and prochlorperazine, but few had received any other treatment. Perhaps greater scatter and lack of prognostic significance of later measurements of PEP/EP are a result of the confounding influence of the varied forms of treatment which the patients received increasingly as time progressed in hospital.

In any survey of a disease it is necessary to consider the extent to which the cases presented are typical of the condition as it exists in the community. An element of selection is inevitable in any study which is hospital-based. Nevertheless, the patients in the present study have been consecutive admissions to a district general hospital, largely via a public accident department. The patients probably represent a wide spectrum of the disease. The converse may apply where a selective admissions policy operates. A feature which should be emphasised in this connection is that the average patient on entry to the present study had already survived the first 12 hours of the disease. During this early phase, particularly the prehospital period, there is a substantial mortality. It would be interesting to know whether these early deaths may be predicted from the measurement of systolic time intervals. This information, however, will be difficult to obtain.

Many of the features of patients with acute myocardial infarction which have been shown by previous investigators to be associated with a poor prognosis have been found to occur more frequently in patients with poor rather than with good left ventricular pumping effectiveness in the present study. The pathophysiological mechanisms which account for these associations are largely unknown and merit further investigation. Prior myocardial infarction or female sex were associated with increased mortality among groups 3 to 6 combined but not among groups 1 and 2 combined. This suggests that the mortality risk associated with these features depends upon the prevailing pumping effectiveness of the left ventricle, but this does not seem to have been noticed previously. Failure to take account of this factor may explain some of the conflicting reports on this subject which have been published. The situation with right bundle-branch block and third degree atrioventricular block was simpler, since both features seemed to constitute statistically significant mortality risk factors which were independent of the level of left ventricular pumping effectiveness. Previous workers have pointed out that these defects in the spread of the cardiac action potential were associated with a high mortality in patients with acute myocardial infarction.[44–50] Again, the available evidence does not permit conclusions regarding the pathophysiological mechanisms responsible for the increased mortality. This merits further investigation, as does the question of whether or not electrical pacing or pharmacological interventions would improve the survival of these patients.

The author acknowledges the co-operation of many members of the staff of the Leicester Royal Infirmary, in particular the encouragement of Dr J R Hearnshaw.

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Serum creatine kinase B subunit activity in diagnosis of acute myocardial infarction

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SUMMARY The value of serum creatine kinase B subunit activity (CK B) in the diagnosis of acute myocardial infarction was studied in 238 consecutive cases. All were admitted to a coronary care unit because of suspected acute myocardial infarction. Serum CK B activity was determined by an immunoinhibition procedure, using a CK M subunit inhibiting antibody (anti-M). For the evaluation of serum CK B, patients were classified into acute myocardial infarction and non-acute myocardial infarction groups. This classification was based on electrocardiographic findings, on quantitative determinations of serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total serum creatine kinase (CK) activities, and on qualitative electrophoretic determinations of serum CK and serum lactate dehydrogenase (LD) isoenzymes. The prevalence of acute myocardial infarction in the patient material was 0·47. Serum CK B subunit activity was found to be a highly selective indicator of acute myocardial infarction with a predictive value of a positive test result of 0·97 and a predictive value of a negative test result of 0·99.

The serum CK B activity increased above the acute myocardial infarction discrimination limit within 12 hours from onset of symptoms.

Two non-acute myocardial infarction patients, who were resuscitated after cardiac arrest, had increased serum CK B values caused by the transient presence of CK isoenzyme BB in serum.

Increase of CK* isoenzyme MB activity in human serum as an indicator of acute myocardial infarction has been well documented.[1–6] Previously reported methods for the determination of CK isoenzymes have most often been based upon either electrophoretic or chromatographic procedures.[7–11] More recently, radioimmunoassays[12 13] and other immunological procedures[14] have been developed. We use an immunoinhibition method for determination of CK B subunit dependent activity in human serum.[15] The application of this immunoinhibition procedure in a group of patients with suspected acute myocardial infarction has been evaluated previously.[16] The aim of the present study was to obtain further data on the diagnostic ability of the serum CK B determination when used as an indicator of acute myocardial infarction. The clinical usefulness of the assay is compared with that of more traditional enzyme tests and the electrocardiogram.

Subjects and methods

Included in the study were 238 consecutive cases admitted to a coronary care unit with symptoms indicative of an acute myocardial infarction within the previous 24 hours. Blood samples were drawn on admission and thereafter at six-hour intervals. On each occasion, two samples were centrifuged within one hour. The serum from one was stored at 4°C for a maximum of 12 hours before determination of serum AST, ALT, and LD. LD activity, however, was often determined at less frequent intervals. The serum from the other sample was frozen at −80°C, immediately after centrifugation, for subsequent total CK and CK B determinations. Measurements of total CK, AST, ALT, and LD were performed according to the SCE† recommended methods.[17 18] CK B subunit

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* Unofficial abbreviations:
CK, creatine kinase; EC 2.7.3.2.
AST, aspartate aminotransferase; EC 2.6.1.1.
ALT, alanine aminotransferase; EC 2.6.1.2.
LD, lactate dehydrogenase; EC 1.1.1.27.

Received for publication 3 July 1979

† Scandinavian Committee on Enzymes of the Scandinavian Society for Clinical Chemistry and Clinical Physiology.

dependent activity was determined as residual CK activity in the SCE CK reaction system after immunoinhibition with a CK M subunit inhibiting antibody (anti-M).[15]

In the first 113 cases, serum CK B analyses were performed after storage of the samples at –80°C for up to four months. Total serum CK, however, was determined within 24 hours. In the subsequent 125 patient cases, both total serum CK and serum CK B determinations were carried out within 24 hours.

Control experiments were performed to determine the decrease of serum CK B activity during four months' storage at –80°C. Twenty-four sera, analysed within 24 hours, showed serum CK B activities that ranged from 9 to 146 U/l. They were then stored at –80°C for four months, after which serum CK B activities were redetermined. The decrease in serum CK B activity averaged 9 per cent and was at most 18 per cent in a single sample.

Serum CK and LD isoenzymes were qualitatively estimated by agarose gel electrophoresis at or around peak total activities of serum CK and LD, respectively. Serum CK isoenzymes were evaluated by NADPH fluorescence after the agarose slides had been incubated with the SCE CK reaction medium.[19] The detection limit for the CK MB isoenzyme with this procedure was approximately 20 to 25 U/l, estimated by electrophoresis of dilutions of known activities from a nearly pure CK MB preparation from human heart tissue. Serum LD isoenzymes were estimated by the tetrazolium method.[20]

DISCRIMINATION VALUES AND DIAGNOSTIC CRITERIA

The discrimination values and diagnostic criteria, respectively, of the different tests are shown in Table 1. The discrimination value for total serum CK and the diagnostic criteria for the qualitative, electrophoretic estimations of CK isoenzyme MB and LD isoenzyme H_4, respectively, were selected on the basis of a previous study.[21] In order to avoid too many false-positive total serum CK results, the acute myocardial infarction discrimination limit for this test was set 40 per cent higher than the upper reference limit in a group of healthy male blood donors.

Table 1 *Different tests to be evaluated; discrimination values and diagnostic criteria used for classification of patients into acute and non-acute myocardial infarction groups*

Tests	*Discrimination values and diagnostic criteria*
Total serum CK	⩾350 U/l
Serum CK B	⩾ 12 U/l
Serum CK MB (electrophoretic estimation)	Demonstrable on CK electrophoresis
Serum AST and ALT	Two AST values > 40 U/l with maximal activity about 24 hours after onset of symptoms; AST > ALT about 36 hours after onset of symptoms
Serum LD H_4 (electrophoretic estimation)	Increased on LD electrophoresis
Electrocardiogram	"Diagnostic" (see text)

The diagnostic criterion for the serum AST-ALT relation, hereafter called AST, was that used in the coronary care unit. The acute myocardial infarction discrimination value for serum CK B activity, determined by the present immunoinhibition method, was selected on the basis of data previously published by us.[16] The standard 12 lead electrocardiogram was considered diagnostic of an acute myocardial infarction if one or more of the following characteristics were present:

(1) Development of a pathological Q wave in two or more leads.
(2) Development, or regression, of a localised ST segment elevation followed by T wave inversion in two or more leads.
(3) Development of a pathological R progression in praecordial leads.

CLASSIFICATION OF PATIENTS

Independently of the serum CK B results, patients were classified into acute myocardial infarction and non-acute myocardial infarction groups. For this classification the following three systems were used.

(1) Classification based on the following five tests: (a) total serum CK; (b) serum CK MB (electrophoretic estimation); (c) serum LD H_4 (electrophoretic estimation); (d) serum AST; and (e) electrocardiogram.

The activities of the quantitative enzyme tests in this system were the maximal values measured in each individual patient. Electrophoretic estimations of serum CK MB and serum LD H_4 were carried out on samples at or around peak total activities of CK and LD, respectively. If any four of the five tests were positive, the patient was classified as a case of acute myocardial infarction. Conversely, if any four were negative, the patient was classified as a case of non-acute myocardial infarction.

(2) Classification according to necropsy findings. Patients were classified as cases of acute myocardial infarction if an infarct of fitting age was found at necropsy.

(3) Classification according to the WHO criteria for definite acute myocardial infarction.[22] In doubtful cases, however, the results of the electrophoretic determination of the CK isoenzyme MB were also taken into acount.

All but 11 patients were classifiable according to (1) or (2). Among these, there were no discrepancies between the classification systems applied. The 11 remaining cases, constituting 5 per cent of the total patients, were classified according to (3).

The independent ability of the serum CK B determination to classify patients into these groups was then investigated and expressed as predictive values of positive and negative test results (see below). For comparison with serum CK B the discrimination abilities of each of the other enzyme tests and of the electrocardiogram were also assessed. When evaluating tests other than serum CK B, patients were divided into acute myocardial infarction and non-acute myocardial infarction groups according to the classification systems described above. However, when applying system (1) patients were defined as cases of acute myocardial infarction if, without reference to the particular test being evaluated (total serum CK, serum CK MB, serum LD H_4, serum AST, and electrocardiogram) at least three of the four remaining tests were positive. Conversely, they were characterised as non-acute case of myocardial infarction if, without reference to the particular test being evaluated, at least three of the four remaining tests were negative. Consequently, serum CK B was never used for classification into acute myocardial infarction and non-acute myocardial infarction groups, as the principal aim of the study was to evaluate this particular test.

PREDICTIVE VALUES OF INDIVIDUAL TESTS

The diagnostic ability of the five enzyme determinations (total CK, CK B, AST, CK MB electrophoretically, LD H_4 electrophoretically) and of the electrocardiogram was expressed as predictive values of each test, calculated according to the principles of conditional probability (Bayes' theorem).[23]

Predictive value of a positive test result (PV pos)

$$= \frac{\text{No. of diseased subjects with positive test result}}{\text{No. of all subjects with positive test result}}$$

Predictive value of a negative test result (PV neg) =

$$\frac{\text{No. of non-diseased subjects with negative test result}}{\text{No. of all subjects with negative test result}}$$

Results

TIME COURSE OF ENZYME PATTERNS IN SOME PATIENTS

Enzyme patterns from some patients are graphically shown in Fig. 1 to 4. Fig. 1 represents a 67-year-old woman who suffered chest pain two to three hours before admission. With the discrimination limits, total CK, AST, and LD were increased by factors of up to about 5, 6, and 3, respectively. Serum ALT was only slightly increased. Electrophoretically, CK MB was detectable and LD H_4 was increased. On the basis of these enzyme data this patient was classified as having acute myocardial infarction, even though the electrocardiogram was not conclusive for an acute myocardial infarction. Serum CK B results were in accord with the diagnosis of acute myocardial infarction, being increased to a maximal value of about five times the discrimination limit.

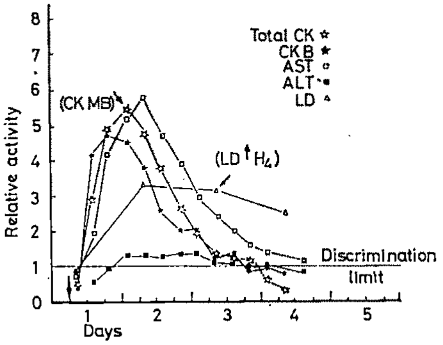

Fig. 1 *Enzyme pattern of a 67-year-old woman with acute myocardial infarction. For case history, see text. Relative activities of enzymes (ordinate) are plotted as a function of time after onset of symptoms, marked by the heavy arrow. The horizontal line at 1 on the ordinate represents the acute myocardial infarction discrimination limit for each enzyme. The curves depict the time courses of the activities in serum of the enzymes total CK, CK B, AST, ALT, and LD, as designated by the symbols on the graph. Symbols in parentheses (CK MB) (LD H_4) indicate the point in time at which a qualitative isoenzyme electrophoresis was carried out.*

Fig. 2 illustrates the clinical sensitivity of the serum CK B method. A 51-year-old woman, with a previous history of ischaemic heart disease, was

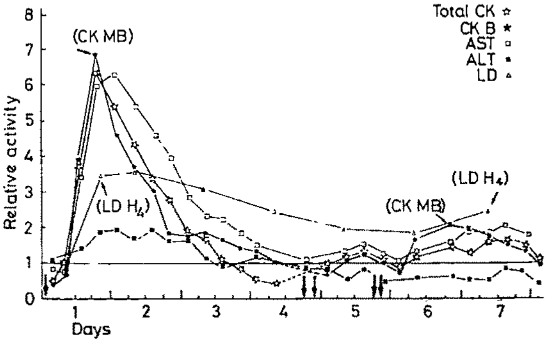

Fig. 2 *Enzyme patterns in a 51-year-old woman with acute myocardial infarction. For case history, see text. For description of symbols see legend to Fig. 1.*

admitted with chest pain starting one hour before admission. Total serum CK and AST activities had increased rapidly to peak values of about six times their respective discrimination limits, by about 18 and 24 hours, respectively, after the onset of pain. Serum ALT activity was constantly lower than that of serum AST. CK MB was electrophoretically demonstrable at peak total serum CK activity, and serum LD H_4 was increased on LD electrophoresis in accord with the diagnosis of acute myocardial infarction. Electrocardiograms showed unequivocal signs of an inferior wall infarct. Serum CK B was in full agreement with the diagnosis of acute myocardial infarction, being rapidly increased to an initial maximal value about seven times the acute myocardial infarction discrimination limit. On the fourth day after admission the patient again suffered repeated attacks of chest pain (arrows in figure). These attacks were followed by increased activities of serum CK B, total serum CK, and serum AST above their respective discrimination limits. On the fifth day after admission new attacks of chest pain occurred (arrows in figure). This episode of pain was also followed by distinctly increased activities of serum CK B, total CK, and AST.

Consequently, in this case serum CK B, as well as total serum CK and AST, permitted demonstration of three episodes of myocardial enzyme release during seven days.

Fig. 3 illustrates the ability of the serum CK B method to distinguish between enzyme release from myocardial and skeletal muscle tissue. A 63-year-old man was admitted with symptoms suggesting acute myocardial infarction during four hours before arrival. According to the criteria described above he was classified as a case of acute myocardial infarction. Within 24 hours after admission, total serum CK, serum CK B, serum AST, and serum LD were increased by factors of about 4, 4, 3, and 2, relative to their respective discrimination limits. Serum ALT constantly remained around the discrimination limit. Shortly after admission, the patient developed ventricular arrhythmias which were treated with procainamide administered intramuscularly at four-hour intervals (arrows in Fig. 3). As long as these repeated intramuscular injections were given, total serum CK activity remained high. After the injections were discontinued, total serum CK activity rapidly decreased. Conversely, serum CK B activity was not influenced by the injections, but showed a rapidly decreasing activity after the initial peak.

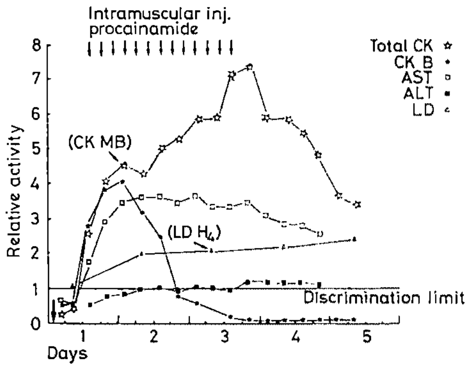

Fig. 3 *Enzyme patterns in a 63-year-old man with acute myocardial infarction. For case history, see text. For description of symbols, see legend to Fig. 1.*

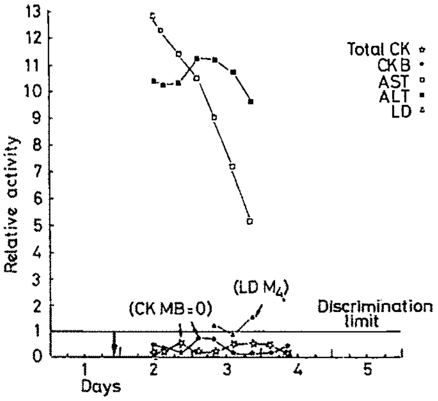

Fig. 4 *Enzyme patterns in a 75-year-old man without acute myocardial infarction. For case history, see text. For description of symbols, see legend to Fig. 1.*

Comment

The serum CK B curve indicated that enzyme release from injured myocardial tissue ceased early in the course of the disease. Conversely, the prolonged increase of the total serum CK activity probably reflected enzyme release from skeletal muscle after the intramuscular injections.

Fig. 4 demonstrates the clinical specificity of serum CK B. A 75-year-old man was admitted to the coronary care unit with chest pain which had lasted 12 hours. Total serum CK was not increased above the acute myocardial infarction discrimination limit and CK MB was not electrophoretically demonstrable. Serum AST and ALT were already high at admission, but declined during the observation period. The AST/ALT relation changed early, serum ALT exceeding AST about 24 hours after onset of symptoms. This was not characteristic of an acute myocardial infarction but rather indicated the liver as the source of enzyme release. This was further supported by an increased LD M_4

isoenzyme fraction and a normal LD H_4 fraction on LD electrophoresis about 48 hours after the onset of symptoms. On the basis of these enzyme data, the patient was classified as having no acute myocardial infarction. This was supported by the electrocardiographic findings which showed no signs of myocardial injury. Serum CK B, by remaining well below the discrimination limit throughout the observation period, also lent support to this diagnosis. Among other laboratory data, there was a very high S-bilirubin and a biliary tract occlusion was later demonstrated.

CLASSIFICATION OF PATIENTS

According to the criteria for acute myocardial infarction and non-acute myocardial infarction, mentioned above, the total 238 cases were classifiable into 113 with acute myocardial infarction and 125 with non-acute infarction. The prevalence of acute myocardial infarction was 0·47.

PREDICTIVE VALUES OF DIFFERENT TESTS

Predictive values of the different tests are shown in Table 2. All tests, except the electrocardiogram, showed relatively high predictive values for a negative test. The electrocardiogram had the poor predictive value for a negative test result of 0·74, because of a high proportion of false negative electrocardiograms. The predictive value for a negative test of serum CK B was 0·99, corresponding to 1 per cent false negatives. The predictive values for positive tests of serum AST and of total serum CK were relatively poor as a consequence of a fairly high proportion of false positive serum AST and total serum CK results.

Table 2 *Predictive values of each test*

	Neg	*Pos*	
AMI	1	112	113
Non-AMI	121	4	125
Total	122	116	238

S-CK B PV pos 0·97
PV neg 0·99

	Neg	*Pos*	
AMI	3	110	113
Non-AMI	125	0	125
Total	128	110	238

CK MB PV pos 1·0
PV neg 0·98

	Neg	*Pos*	
AMI	5	108	113
Non-AMI	106	19	125
Total	111	127	238

Total S-CK PV pos 0·85
PV neg 0·95

	Neg	*Pos*	
AMI	1	112	113
Non-AMI	110	15	125
Total	111	127	238

S-AST PV pos 0·88
PV neg 0·99

	Neg	*Pos*	
AMI	7	106	113
Non-AMI	123	2	125
Total	130	108	238

LD H_4 PV pos 0·98
PV neg 0·95

	Neg	*Pos*	
AMI	43	70	113
Non-AMI	125	0	125
Total	168	70	238

ECG PV pos 1·0
PV neg 0·74

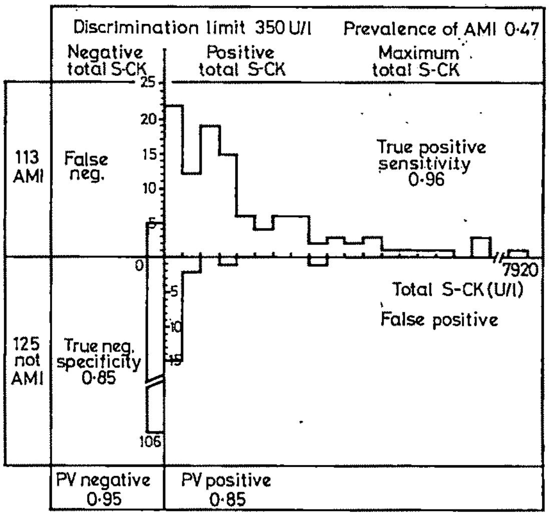

Fig. 5 *Frequency histogram of maximal total serum CK activities in each of 113 cases with acute myocardial infarction and 125 cases with non-acute myocardial infarction.*
Abscissa: *Total serum CK activities in steps of 350 U/l. The discrimination limit of 350 U/l is at the intersection with the ordinate. "Negative" total serum CK activities to the left of the ordinate, "positive" total serum CK activities to the right.*
Ordinate: *Number of patients within each total serum CK interval can be read from height of each column.*
Classification: *Acute myocardial infarction cases* upper panel. *Non-acute myocardial infarction cases,* lower panel.
Correlation: *False-negative and true-positive total serum CK values in left and right upper quadrants, respectively. True-negative and false-positive total serum CK values in left and right lower quadrants, respectively.*

The predictive values for other positive tests were relatively high: that for serum CK B was 0·97. False positive serum CK B results were obtained in four cases which will be discussed separately below.

Comment

The predictive values for the electrophoretic estimations of serum CK MB and LD H_4 were unexpectedly high, probably because the electrophoreses were consistently carried out on one or more samples at or around peak total activities of serum CK and LD, respectively.

DISTRIBUTION OF TOTAL SERUM CK AND SERUM CK B ACTIVITIES

Fig. 5 shows the distribution of the maximal total serum CK value from each of the 238 patient cases. Fig. 6 shows the corresponding data for the serum CK B values. The two histograms permit identification of the number of false and correct results obtained by the two enzyme tests.

ENZYME ACTIVITIES IN RELATION TO TIME AFTER ONSET OF ACUTE SYMPTOMS

In 55 patients with acute myocardial infarction with increased activities of serum CK B, total CK, and AST above their respective discrimination limits, we were able to define distinctly the time when the acute symptoms began. The enzyme data of these patients were used to illustrate the probabilities of serum CK B, total CK, and AST being increased above their respective discrimination limits at a certain time after the onset of acute symptoms. Fig. 7 shows the patients with acute myocardial infarction who had CK B activities above the discrimination limit of 12 U/l, as a function of time after the onset of symptoms. Fig. 8 and 9 show the corresponding data for total serum CK and AST, respectively. Serum activities of CK B and total CK of all patients exceeded the discrimination limits within 12 hours after the onset of symptoms. The corresponding time for serum AST was 16 hours. On the other hand, serum activities of CK B and total CK returned to below the respective discrimination limits earlier than those of AST. This is illustrated in Fig. 7 and 8 by the decreasing number of patients with serum CK B and total serum CK activities above their respective discrimination limits at 22 and 16 hours after the onset of symptoms. For comparison, all patients still had increased serum AST values 36 hours after onset of symptoms (Fig. 9).

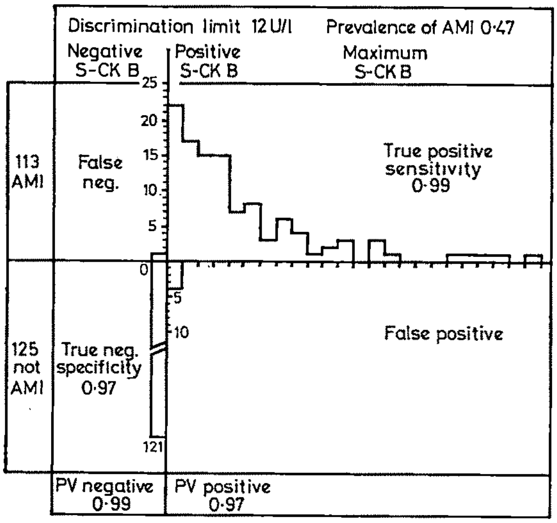

Fig. 6 *Frequency histogram of maximal serum CK B values in each of 113 cases with acute myocardial infarction and 125 cases with non-acute myocardial infarction.*

Abscissa: *Serum CK B activities in steps of 12 U/l. The discrimination limit of 12 U/l is at the intersection with the ordinate. "Negative" serum CK B activities to the left of the ordinate, "positive" serum CK B activities to the right.*

Ordinate, classification, correlation: *See legend to Fig 5*

Discussion

As long-term frozen sera were used for determination of serum CK B activities in 113 of the 238 cases, we studied the decrease in serum CK B activity during storage for four months at –80°C (see above). Data from these control experiments, together with the serum CK B results obtained in long-term frozen sera, indicated that storage under the described conditions did not change the CK B activities sufficiently to influence the predictive values obtained for this test. Consequently, we were able to use samples from all the patients when evaluating serum CK B.

Use of serum CK B activity, as an indicator of acute myocardial infarction, presupposes that all CK B subunit dependent activity in serum derives from myocardial CK isoenzyme MB. The possible occurrence of CK isoenzyme BB in human serum therefore implies a potential risk of a CK BB induced rise in serum CK B activity being mistaken for a manifestation of acute myocardial infarction. Consequently, in order to optimise the diagnostic power of the serum CK B determination, it is important to be aware of some clinical conditions in which CK BB may be present in serum. Detectable serum CK BB activity is reported in a variety of conditions, even if opinions concerning the occurrence of this isoenzyme in many of these instances are contradictory.

Conditions recurringly reported as possible causes of serum CK BB activity are cerebral diseases and injuries,[24–26] some malignant diseases,[27–29] chronic uraemia, [30–32] some nervous system disorders, such as "floppy infant syndrome", and Werdnig-Hoffman's disease.[33] Most of these conditions, however, do not present any differential diagnostic problems in relation to acute myocardial infarction. Another cause of detectable serum CK BB activity is anoxic brain injury after cardiac arrest.[24 25] In this situation, an increased serum CK B value may be difficult to assess, as it can derive from CK MB, CK BB, or both. The problem is illustrated in two of our patients with false-positive serum CK B results. In both cases increased serum CK B activities occurred as a consequence of the transient presence of CK BB in the serum.

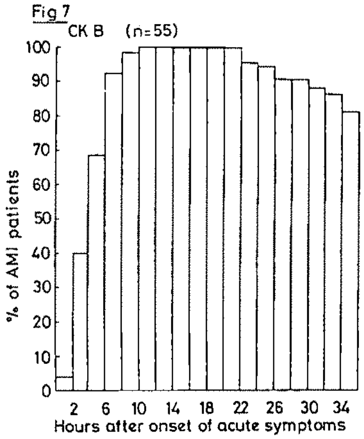

Fig. 7 *Proportion of 55 patients with acute myocardial infarction showing positive serum CK B activities as a function of time after onset of acute symptoms.*
Ordinate: *Percentage of 55 patients with acute myocardial infarction.*
Abscissa: *Time interval (hours) after onset of acute symptoms.*

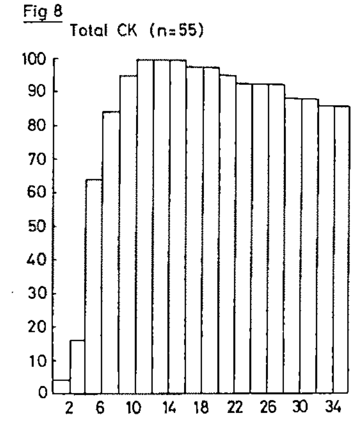

Fig. 8 *Proportion of 55 patients with acute myocardial infarction showing positive total serum CK activities as a function of time after onset of acute symptoms. See also legend to Fig. 7.*

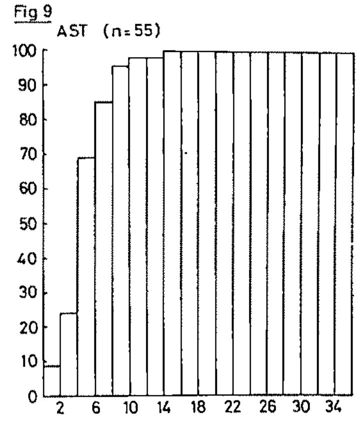

Fig. 9 *Proportion of 55 patients with acute myocardial infarction with positive serum AST activities as a function of time after onset of acute symptoms. See also legend to Fig. 7.*

One of the patients was a 58-year-old man with cardiac arrest (Fig. 10). The electrocardiogram on arrival showed ventricular fibrillation. Normal heart action was immediately restored by defibrillation. The patient survived, but remained unconscious for about 20 hours after resuscitation; continuous electrocardiographic monitoring disclosed frequent ventricular arrhythmias. The enzyme data, as shown in Fig. 10, with serum ALT activity exceeding that of AST activity, total serum CK activity below the acute myocardial infarction discrimination limit, absence of CK MB on CK electrophoresis, and an increased LD M_4 fraction together with a normal LD H_4 fraction on LD electrophoresis made this patient classifiable as a non-infarction case. This diagnosis was further supported by the electrocardiogram which showed no signs of myocardial damage. The transient serum CK B elevation in the admission sample was a result of the serum CK BB activity, as shown on CK electrophoresis.

We previously described an additional group of patients with CK BB in the serum and consequently increased serum CK B activity.[19] In these patients, the BB isoenzyme had an abnormal electrophoretic mobility and was not associated with any known disease. Such patients are recognised by the combination with increased serum CK B activity despite normal, or close to normal, total serum CK activity. In the present patient series, one patient with non-acute myocardial infarction with false-positive serum CK B result might represent this group. The patient was a 76-year-old woman with a constant slightly increased serum CK B activity of about 12 to 14 U/l in spite of normal total serum CK and other enzyme activities. On serum CK electrophoresis only regularly migrating isoenzyme MM was visible while no isoenzyme band corresponding to the increased serum CK B activity was shown. This, however, might be a consequence of the relatively low serum CK B activity which corresponds to BB isoenzyme

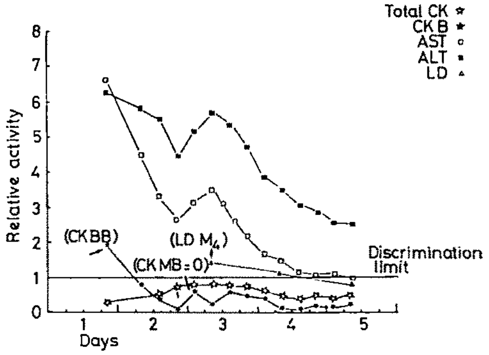

Fig. 10 *Enzyme patterns in a 58-year-old man with cardiac arrest but no acute myocardial infarction. For case history, see text. For description of symbols, see legend to Fig. 1.*

activity which may fail to reach the detection limit of the electrophoretic procedure.

The remaining false-positive serum CK B result appeared in a patient suffering from repeated attacks of chest pain with concomitant electrocardiographic abnormalities of the Prinzmetal variant angina type. According to the applied classification systems he was classified as a case of non-acute myocardial infarction. However, it is possible that the transient and slight increase in serum CK B activity corresponded to a true but very small myocardial infarction.

The main advantage of the serum CK B analysis, as compared with total serum CK and serum AST determinations, is the increase of the predictive value of a positive test result because of the lower proportion of false-positive results. The relatively poor predictive values of a positive test result of total serum CK and AST mainly reflect the fact that these serum enzyme activities are influenced by many non-cardiac conditions. Thus, total serum CK is often raised after various therapeutic and diagnostic interventions, such as intramuscular injections,[34] and cardioversion.[35] On the other hand, the predictive values of a negative test result of total CK and AST are similar to that of CK B, indicating the same low proportion of false negative results.

The electrophoretic, qualitative estimations of CK and LD isoenzymes gave about the same predictive values as did serum CK B. The electrophoreses were always performed on one or more samples at or around the peak total activities of the respective enzymes, thus giving optimal test conditions. However, electrophoretic estimation of LD isoenzymes may be particularly useful in patients with delayed admission after the onset of symptoms indicating an acute myocardial infarction. In such cases, the determinations of total serum CK and serum CK B are less suited for the diagnosis of acute myocardial infarction, caused by the transient nature of their serum activity increases after an acute myocardial infarction.[36]

In conclusion, the serum CK B determination is a test of high clinical specificity and sensitivity in the early diagnosis of acute myocardial infarction. The method is relatively simple and rapid, and is well suited for the routine clinical laboratory.

Note added in proof

A complete description of the updated method for serum CK B determination using an improved CK M subunit antibody has recently been published.[37]

This investigation was supported by grants from the Thorsten and Elsa Segerfalk's Foundation, Helsingborg, from the Malmöhus läns Allmzänna försäkringskassa, and from Mrs Maria Embring, Helsingborg.

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Br Heart J 1980; **43:** 523–6

Salbutamol in cardiogenic shock complicating acute myocardial infarction

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SUMMARY Intravenous salbutamol (13 μg/min) has been given to 31 patients with cardiogenic shock complicating acute myocardial infarction. Haemodynamic measurements were made in nine of these patients. Salbutamol increased cardiac index by 41 per cent from 1·25±0·06 l/min per m^2 to 1·76±0·19 l/min per m^2 and decreased systemic vascular resistance by 16 per cent from 26·2±1·9 units to 21·9±2·1 units. Heart rate rose by 13 per cent from 95±4·5 beats/min to 106±6·0 beats/min. Pulmonary artery end-diastolic pressure fell from 20·6±1·7 mmHg to 16·9±1·9 mmHg. Of the 31 patients, eight survived to leave hospital (27%). Five of the survivors had initial low heart rates and in these patients the clinical improvement was probably attributable to the positive chronotropic action of salbutamol. In the remaining three survivors clinical improvement was probably a result of salbutamol mediated afterload reduction. Salbutamol may be useful in the treatment of cardiogenic shock and pump failure complicating acute myocardial infarction.

Vasodilator drugs may improve cardiac performance in heart failure after acute myocardial infarction.[1] Cardiac output is increased by a reduction in systemic vascular resistance (afterload) while myocardial oxygen demand falls as a result of reduced left ventricular wall tension. Salbutamol is a selective beta-2 agonist first introduced for the treatment of bronchial asthma.[2] Animal experiments suggest that its principal cardiovascular effect is a relaxation of vascular smooth muscle producing vasodilatation.[3 4] In man, though the exact mechanism is uncertain, beneficial haemodynamic effects with intravenous salbutamol have been described in patients with mitral valve disease,[5] in low output states after cardiac surgery,[6–8] and in congestive cardiomyopathy.[9]

Lal *et al.*[10] treated 12 patients with cardiogenic shock after acute myocardial infarction with intravenous bolus injections of salbutamol (1 to 2 mg). Their report, which does not include haemodynamic data, describes clinical improvement in nine patients, six of whom survived to leave hospital.

We have treated 31 patients with cardiogenic shock after acute myocardial infarction with intravenous salbutamol, and describe the clinical outcome, as well as the haemodynamic responses in nine of them.

Received for publication 23 July 1979

Patients

Thirty-one patients with cardiogenic shock complicating acute myocardial infarction comprise the series. Cardiogenic shock was defined as systolic hypotension (<90 mmHg) associated with oliguria (urine output less than 30 ml/h). All had clinical evidence of low cardiac output (peripheral vasoconstriction and disturbances of consciousness). Twenty-seven patients had radiological evidence of pulmonary oedema. In all patients intravenous frusemide (80 to 500 mg) had been ineffective in promoting a diuresis.

Nineteen patients had anterior and 12 had inferior infarcts; 14 had a previous history of angina or myocardial infarction. Sinus rhythm was present in 24 patients, three were in atrial fibrillation, and four were undergoing temporary pacing for complete heart block complicating the acute infarct.

All patients were given salbutamol by continuous intravenous infusion in a dose of 13 μg/min. Haemodynamic measurements were made at the patient's bedside in the coronary care unit in nine patients (six men, three women; age range 52 to 68, mean 59) eight of whom were in sinus rhythm, while one was being paced at a fixed ventricular rate of 90 for complete heart block. In the remaining 22 patients (17 men, five women; age range 52 to 72, mean 59) the response to salbutamol was assessed by clinical observation together with measurements of heart rate, blood pressure, and urine output.

Haemodynamic measurements

A Swan-Ganz thermodilution catheter (CVI Model No. 600-017) was inserted percutaneously into the right subclavian vein and advanced to the pulmonary artery. Measurements were made of right atrial, right ventricular, pulmonary artery, and wedge pressures. The sternal angle was used as the zero reference point. In all patients pulmonary artery end-diastolic pressure (PAEDP) was found to correlate closely with wedge pressure and in order to avoid frequent catheter manipulations PAEDP was used in most subsequent recordings as an indirect assessment of left ventricular filling pressure. Cardiac output was measured by the thermodilution technique[11] using a cardiac output computer (CVI Model No. 600). The injectate was 10 ml normal saline at room temperature. Each value for cardiac output was derived from the average of at least three estimations. Systemic arterial pressure was recorded with an Infrasonde electronic sphygmomanometer (Model No. 3000). Mean arterial pressure was calculated as the diastolic pressure plus a third of the pulse pressure. Heart rate was obtained from an electrocardiogram recorded simultaneously with each measurement of intracardiac pressure and was averaged over 20 beats. Intravenous salbutamol (10 mg in 500 ml, 5% dextrose) was given in a dose of 13 μg/min, the infusion rate being controlled by a Tekmar 51 pump. The intracardiac pressures, cardiac output, heart rate, and arterial pressure were recorded at the beginning and end of a 20-minute control period and then at 10, 20, and 40 minutes after the start of the salbutamol infusion. Cardiac index, stroke index, and systemic vascular resistance

$$\frac{\text{mean arterial pressure} - \text{mean right atrial pressure}}{\text{cardiac output}}$$

were calculated. The results recorded are at the end of the control period and at 40 minutes from the start of salbutamol infusion and values are compared using Student's paired t test.

Results

In nine patients who had haemodynamic measurements, the changes induced by salbutamol are shown in the Figure. Cardiac index rose in all patients from 1·25 ± 0·06 l/min per m^2 to 1·76 ± 0·19 l/min per m^2 (41%, $p < 0·002$). Stroke index increased by an average of 28 per cent from 13·2 ± 0·74 ml/beats per m^2 to 16·9 ± 1·4 ml/beat per m^2 ($p < 0·005$). Heart rate rose by an average of 13 per cent from 95 ± 5 beats/min to 107 ± 6·6 beats/min ($p < 0·05$). Systemic vascular resistance fell from 26·2 ± 1·9 units to 21·9 ± 2·1 units (16%, $p < 0·02$).

Pulmonary artery end-diastolic pressure fell from 20·6 ± 1·7 mmHg to 16·9 ± 1·9 mmHg after salbutamol (18%, $p < 0·05$). There was a small, though insignificant, increase in mean arterial pressure from 64·8 ± 4·1 mmHg to 70·3 ± 4·7 mmHg. After completion of the haemodynamic measurements, all these patients continued treatment with intravenous salbutamol. Two patients (one with an anterior and one with an inferior infarct) survived to leave hospital. In this group there were no appreciable differences in the initial haemodynamic indices between the two survivors and the seven non-survivors. In one patient, a non-survivor, the salbutamol infusion had to be stopped because of the development of supraventricular tachycardia; this was the only complication in the series.

In the 22 patients who did not have haemodynamic measurements there were similar changes in heart rate and mean arterial pressure. Excluding the three patients who were being paced for complete heart block, the heart rate rose from 88 ± 5·8 beats/min to 101 ± 4·9 beats/min (average 15%, $p < 0·001$). Mean arterial pressure did not change significantly (mean 71 ± 3 mmHg before, and mean 74 ± 3 mmHg) (average 4%). Six patients from this group (four with inferior and two with anterior infarcts) survived to leave hospital. Initial heart rate (63 ± 2·5 beats/min) was significantly lower in the survivors than in the non-survivors (99 ± 9·1 beats/min) ($p < 0·005$).

Urine output was measured in all patients and increased from a mean of 9 ± 1·7 ml/h to a mean of 72 ± 22·6 ml/h after salbutamol ($p < 0·01$).

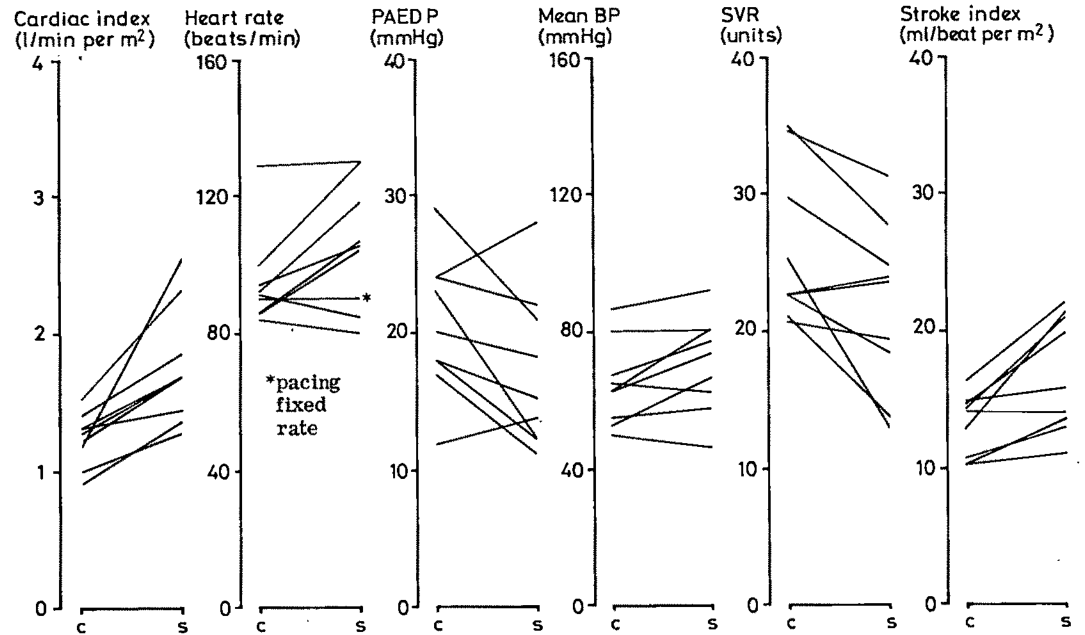
Discussion

Clinical evidence of cardiogenic shock with pump failure was present in all patients with systemic hypotension, peripheral vasoconstriction, oliguria, and in most cases pulmonary oedema. In nine patients in whom haemodynamic measurements were made, the extremely low initial cardiac outputs further emphasise the severity of pump failure present in these patients. Salbutamol significantly increased cardiac index, stroke index, and heart rate while reducing systemic vascular resistance and left ventricular filling pressure. The percentage rises in cardiac index (41%) and fall in systemic vascular resistance (16%) are similar to those changes noted by ourselves,[12] and by Sharma and Goodwin[9] in patients with chronic heart failure treated with intravenous salbutamol. The increase in heart rate (13%) is similar to that found by Gibson and Coltart[5] in patients with mitral valve disease and by Poole-Wilson *et al.*[8] in patients after open heart surgery but was a less striking feature of our patients with chronic heart failure.

The exact mode of action of salbutamol on the human cardiovascular system is not clearly established. Cullum *et al.*[3] working with animals, showed that salbutamol has 1/10 the activity of isoprenaline on vascular smooth muscle but only 1/2000 its activity in increasing heart muscle tension. This implies that the increased cardiac output noted with salbutamol is principally a result of vasodilatation secondary to beta-adrenergic stimulation of vascular smooth muscle rather than a direct cardiac effect. This finding, that salbutamol has a negligible effect on heart muscle beta-adrenergic receptors, was confirmed by Nayler[4] working with isolated human heart muscle preparations. In addition, Nayler showed that in dog preparations there was evidence of salbutamol mediated direct coronary artery dilatation which is not dependent upon an increase in myocardial oxygen demand. The results of these in vitro experiments tend to conform with the findings in the majority of reports on patients with heart disease,[5 7 8 12] though Sharma and Goodwin,[9] whose patients had congestive cardiomyopathy, concluded that salbutamol induced increases in cardiac output are a result of positive inotropic stimulation.

We believe that the increased cardiac output observed in our patients was probably a result of vasodilatation rather than a positive inotropic effect. In preparations of isolated rabbit papillary muscle the minimum concentration of salbutamol required to produce a positive inotropic effect is 0·09 mg/l,[12] 10 times the estimated serum concentration of salbutamol in man that would be achieved by an infusion rate of 13 μg/min.

An increase in heart rate was observed in the majority of our patients and appears to have been beneficial in some, though excessive increases in



	Cardiac index c	Cardiac index s	Heart rate c	Heart rate s	PAEDP c	PAEDP s	Mean BP c	Mean BP s	SVR c	SVR s	Stroke index c	Stroke index s
Mean	1·25	1·76	95·0	107·0	20·6	16·9	64·8	70·3	26·2	21·9	13·2	16·9
SE	0·06	0·19	5·0	6·6	1·7	1·9	4·1	4·7	1·9	2·4	0·74	1·4
% change	41		13		18		9		16		28	
p<	0·002		0·05		0·05		NS		0·02		0·005	

c = control s = salbutamol 13μg/min

Fig. *The changes in cardiac index, heart rate, pulmonary artery end-diastolic pressure (PAEDP), mean blood pressure (BP), systemic vascular resistance (SVR), and stroke index with salbutamol.*

heart rate may be detrimental to an already ischaemic myocardium by increasing myocardial oxygen consumption.[13] The mechanism of the increase in heart rate was not determined.

In this study, eight patients (27%) survived to leave hospital. This survival rate is similar to previously reported rates in patients with cardiogenic shock complicating myocardial infarction.[14] In five of the survivors (four inferior and one anterior infarct) initial heart rate was inappropriately low. The chronotropic action of salbutamol may have been responsible for the clinical improvement observed in these patients. In the remaining three survivors (two anterior and one inferior infarct) initial heart rate was high (mean 92 beats/min), and in the two patients for whom haemodynamic data are available the initial haemodynamic indices in survivors were the same as in non-survivors. In these patients improved cardiac performance was probably mediated by salbutamol induced afterload reduction. Though a non-survivor, one patient who had measured haemodynamic responses was being paced for complete heart block. This patient had similar increases in cardiac output and stroke index, and similar falls in systemic vascular resistance and left ventricular filling pressure as the remaining eight patients, though heart rate of course remained constant.

Vasodilators are now widely advocated in the treatment of pump failure after acute myocardial infarction though survival rates are low. Sodium nitroprusside,[15] phentolamine,[16] glyceryl trinitrate,[17] and isosorbide dinitrate[18] have all been shown to have beneficial haemodynamic effects. Our findings suggest that, though survival was disappointingly low in spite of treatment, salbutamol is a valid alternative drug in the management of pump failure and cardiogenic shock complicating acute myocardial infarction.

We thank Allen & Hanbury Ltd for supplying the intravenous salbutamol.

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Br Heart J 1980; **43:** 527–34

Thallium-201 scintigraphy for diagnosis of old myocardial infarction: comparison with electrocardiographic, ventriculographic, and coronary arteriographic findings

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SUMMARY Myocardial scintigraphy with ^{201}Tl was performed at rest in a selected group of 36 patients with unequivocal clinical and electrocardiographic evidence of old myocardial infarction.

The scintigraphic findings were correlated with electrocardiographic pattern, and with regional left ventricular wall motion and the severity of coronary artery disease defined by contrast angiography. Detection was dependent on the extent of the infarct but was independent of QRS morphology and of the severity of coronary disease. When positive, ^{201}Tl scintigraphy was often a more precise method than the electrocardiogram for localising and delineating the extent of the infarct. Furthermore, the perfusion defect corresponded in location and extent to abnormalities of left ventricular wall motion. The site or severity of coronary artery disease could not be determined from the ^{201}Tl scintigram.

Myocardial scintigraphy after intravenous ^{201}Tl injection is widely used for the evaluation of patients with acute myocardial infarction[1–3] and for the assessment of myocardial perfusion during stress testing.[3 4] However, the value of this technique in the detection of old myocardial infarction is still uncertain. While some investigators have reported a high degree of sensitivity,[5 6] poor results were found by others.[7 8] These different findings are probably related to the different selection of patients.

In order to investigate the sensitivity of this technique for the detection and localisation of old myocardial infarction we have studied a selected group of patients with old myocardial infarction defined by clinical, enzymatic, and electrocardiographic criteria. Thus, we were able to assess the relation of perfusion defects, electrocardiographic signs of infarction, abnormalities of the left ventriculograms, and the severity of coronary artery disease.

Subjects and methods

A selected population of 36 patients, aged from 35 to 70 years (mean 54 years), with old myocardial infarction, documented by typical clinical features, and enzymatic and electrocardiographic abnormalities, form the basis of this report. There were 29 men and seven women.

The myocardial infarction had occurred from two months to seven years before this study (mean 13·5 months).

SCINTIGRAPHIC STUDIES

^{201}Tl scintigrams were recorded at rest, in the absence of chest pain or acute electrocardiographic changes.

All scintigrams were recorded using a Jumbo Toshiba gamma camera (mod. 202) with a high sensitivity collimator and a window setting of 20 per cent about the energy peak of ^{201}Tl. The camera field of view was restricted to 12 × 12 cm; within this field a total of 100 000 counts were obtained (equivalent to between 450 and 500 thousand counts per unrestricted field) and recorded "life-size" on *x*-ray film. Imaging was begun five minutes after the intravenous injection of 1 mCi ^{201}Tl,* initially in the left anterior oblique (LAO) projection and then followed, in rapid succession,

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Received for publication 31 August 1979

* Thallium-201 was supplied by Dr R B J de Jong, NV Philips-Duphar, Cyclotron and Isotope Laboratories, Petten, Holland.

by a repeat LAO view and the anterior and left lateral projections. We selected the 45° LAO projection as the single oblique projection providing the most information in the absence of any firm evidence to suggest that multiple oblique projections would be superior. Imaging was completed within 20 minutes of tracer injection and the whole procedure was repeated four hours later.

CORONARY ARTERIOGRAPHY AND LEFT VENTRICULOGRAPHY

Left ventriculography was performed in the right and left anterior oblique projections and recorded on 35 mm film at 50 frames per second. Coronary arteriography, by the Judkins technique, was performed before and after the sublingual administration of glyceryl trinitrate and recorded at 30 frames per second.

ANALYSIS OF DATA

Electrocardiogram

The electrocardiogram was analysed for the presence and location of myocardial infarction according to the criteria of the American Heart Association.[9]

Scintigrams

The films were analysed by two independent observers without knowledge of the electrocardiographic and angiocardiographic findings. In the event of disagreement the scintigrams were analysed by a third observer and agreement reached by at least two of the three observers. The images were graded as normal or abnormal and, from consideration of all projections, the defects were defined as anterior, inferior, posterior, or apical.

The scintigrams of 12 patients were also analysed by a computerised optical densitometer.[10] After background subtraction (estimated from the lung field adjacent to the heart) two types of analysis were made: (1) interimage, between corresponding regions of the pair of early LAO scintigrams; and (2) interwall, between four regions of interest within each scintigram, namely the posterior, inferoposterior, inferoanterior, and anterior walls of the left ventricle. The activity per unit area in each region of interest was calculated and expressed as a percentage of total cardiac activity. The difference between this percentage and that of the region of highest activity was also calculated. Local density was calculated in preference to total regional activity because of the lack of an objective method of determining the boundaries of the left ventricular walls. For the purpose of densitometric analysis, a normal left ventricular wall was defined as that without electrocardiographic or ventriculographic abnormality.

For the purpose of defining normal variability a similar analysis was performed on the normal walls defined by the electrocardiogram and left ventriculogram.

CORONARY ARTERIOGRAPHY AND LEFT VENTRICULOGRAPHY

We noted the pattern of distribution of major coronary vessels to each region of the left ventricle: for the anterior wall and septum the left anterior descending (LAD) with or without the diagonal branches; for the lateral wall, the obtuse marginal branch of the left circumflex; for the inferior wall, the right coronary artery or left circumflex artery. The severity of coronary lesions was classified in the following manner: (1) complete obstruction or stenosis greater than 90 per cent, and (2) stenosis between 75 and 90 per cent (diameter reduction).

The left ventriculograms (RAO and LAO projections) were analysed for the presence and location (anterior, apical, or inferior) of wall motion abnormalities (dyssynergy). The dyssynergy was classified in two groups: (1) dyskinesia (paradoxical systolic wall motion); (2) either akinesia or hypokinesia (designated as "akinesia").

LOCALISATION OF OLD MYOCARDIAL INFARCTS

The localisation of old myocardial infarcts was based on the distribution of QRS abnormalities in the current electrocardiogram. This was compared with the distribution of the ^{201}TI perfusion defects and of the ventriculographic abnormalities.

Results

SCINTIGRAPHIC FINDINGS

There were no consistent differences between corresponding scintigrams obtained within 20 minutes of ^{201}Tl injection and those recorded at four hours. No differences in the replicated LAO scintigrams were found either by visual or densitometric interimage analysis (Table 1). Densitometric

Table 1 *Densitometric analysis*

	No. of patients	*Interimage analysis* (%)	*Interwall analysis* (%)
Normal walls	7	5–13 $\bar{x}$9·33 ±3·5	6–14 $\bar{x}$9·5 ±3·5
Infarcted walls (negative by inspection)	7	5–12 $\bar{x}$9·15 ±3·0	9–21 $\bar{x}$13·1 ±4·3
Infarcted walls (positive by inspection)	5	6–12 $\bar{x}$9·1 ±2·9	25–40 $\bar{x}$30·1 ±10

Results given as range, mean ($\bar{x}$) ± SD.

analysis agreed closely with analysis by inspection for the normal walls, the infarcted walls with homogeneous activity, and the infarcted walls with perfusion defects.

In the seven patients with old myocardial infarction and normal ^{201}Tl scintigrams by visual inspection which were analysed by computer, the variation in activity between the region of infarction as defined by the electrocardiogram and the normal region was $13{\cdot}1 \pm 4{\cdot}3$ per cent. Furthermore, for each of these patients, the percentage of variation was within one SD of the mean for the normal walls. However, five patients with old myocardial infarction and positive ^{201}Tl scintigrams showed a difference in activity of 30, 26, 35, 40, and 25 per cent in the infarcted region compared with the normal region.

Perfusion defects were seen (Fig. 1) in all eight patients with extensive anterior infarction (Fig. 2, 3), in three of 10 with anteroseptal infarction, in five of 13 with inferior infarction, and in three of five with combined anteroseptal and inferior infarction. Among the patients with inferoposterior infarction, both patients with infarction confined to the posterior wall showed unequivocal perfusion defects (Fig. 4).

The presence or absence of a perfusion defect (Fig. 5) was not necessarily related to the electrocardiographic pattern (QS or qR). The incidence of perfusion defects was similar in patients with either a qR or QS pattern, both for inferior and anteroseptal infarcts. In the case of extensive anterior infarction, all patients showed perfusion defects regardless of QRS morphology.

In 10 of the 19 patients with positive scintigrams, ^{201}Tl scintigraphy allowed *more precise* localisation and quantification of the infarct area than was possible from the electrocardiogram. The findings in two of these patients are shown in Fig. 3 and 4. The accuracy of the scintigraphic findings is confirmed by the ventriculographic abnormalities which correspond exactly in extent and location.

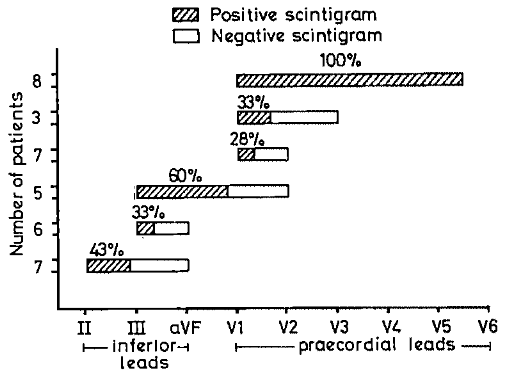

Fig. 1 *Relation of ^{201}Tl scintigraphic findings to the extent of Q waves. On the ordinate, the number of patients in each group. On the abscissa, bars represent the extent of Q waves and the shaded regions represent the positive scintigrams. The proportion of positive scintigrams increases as Q waves become more widespread.*

RELATION OF THALLIUM DEFECTS TO CORONARY ARTERIOGRAMS, ELECTROCARDIOGRAMS, AND LEFT VENTRICULOGRAMS

There were 74 regions supplied by a vessel with greater than 75 per cent stenosis in a total of 36 patients (Table 2). Dyssynergy was present in 46 regions (62%), 10 of which showed dyskinesia; electrocardiographic evidence of infarction was present in 39 (53%) and a ^{201}Tl perfusion defect in 20 (27%). Two of the four regions with Q waves, perfusion defects, and normal wall motion were supplied by normal coronary arteries. ^{201}Tl perfusion defects were usually associated with abnormal wall motion, particularly dyskinesia ($p < 0{\cdot}025$) and, invariably, with Q waves. Nine regions showing akinesia were not associated with Q waves or a perfusion defect but were adjacent to regions of infarction. All the regions with significant coronary disease and without either electrocardiographic or ventriculographic evidence of infarction were ^{201}Tl negative.

Table 2 *Analysis of electrocardiographic, ventriculographic, and scintigraphic findings in regions distal to severe coronary obstruction*

No. of regions	*Q waves*	*Akinesia*	*Dyskinesia*	*Tl defects*
19	+	11	8	+
18	+	16	2	–
1	+	–	–	+
1	+	–	–	–
9	–	9	–	–
26	–	–	–	–

In the 36 patients, no consistent relation was shown between the presence or absence of complete obstruction of the corresponding coronary vessels and the presence or absence of ^{201}Tl perfusion defects (Fig. 6). Furthermore, no such relation was found when all regions with significant coronary disease were examined: perfusion defects were found in six of the 24 regions with greater than 75 per cent stenosis and in 10 of the 42 regions with greater than 90 per cent stenosis or total occlusion of the supplying vessel.

However, in all eight patients with extensive anterior infarction who exhibited a ^{201}Tl perfusion defect, a total coronary occlusion or a stenosis greater than 90 per cent was a consistent finding.

Discussion

The design of the study, with a selection of patients with documented, unequivocal evidence of old myocardial infarction, allowed us to evaluate the diagnostic sensitivity of ^{201}Tl myocardial scintigraphy.

Our results indicate that this technique provides a fair assessment of the location and extent of myocardial tissue loss when the myocardial infarct is large. Under these conditions it appears to correlate better with the ventriculographic than with the electrocardiographic findings. However, this is not the case when myocardial tissue loss is small. In fact, only 54 per cent of the electrocardiographic-defined regions of infarction showed a perfusion defect.

The low incidence of positive scintigrams is not a reflection of the observer's ability to detect regional variations in activity by visual inspection of the original scintigrams. This is clearly illustrated by our results, showing no significant variations in regional activity, quantified by densitometric analysis, in the patients with infarction and negative scintigrams by visual inspection. Furthermore, the results were the same whether the original scintigrams or the computer-processed scintigrams were analysed by visual inspection.

This poor sensitivity may be related to the difficulty in detecting small infarcts, as indicated

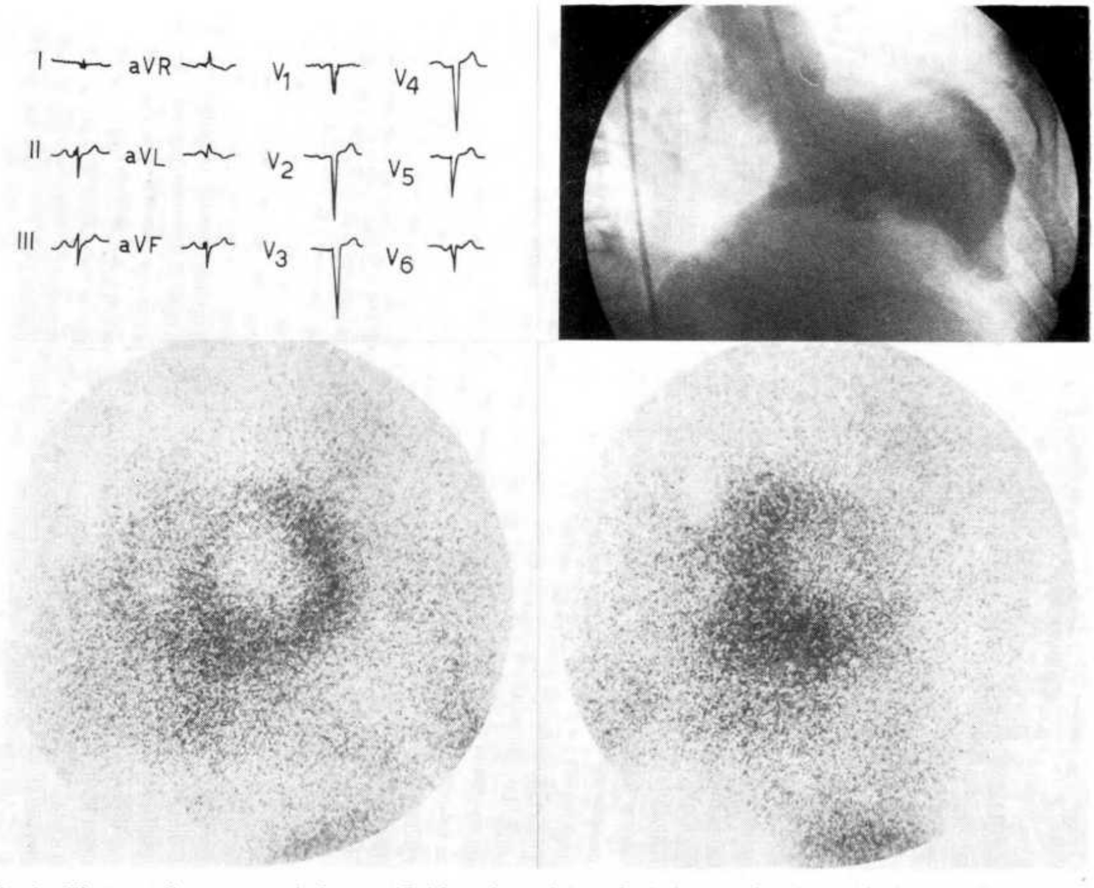

Fig. 2 *Electrocardiogram, ventriculogram (RAO, end-systole), and scintigrams of patient with electrocardiogram-defined, extensive, anterior infarction. LAO scintigram shows an area of reduced activity in the anteroseptal region. In the AP projection the perfusion defect involves the anterolateral wall and apex and corresponds exactly to the site of dyssynergy on the left ventriculogram. The coronary arteriograms showed greater than 90 per cent stenosis of the left anterior descending artery.*

by experimental work showing that infarcts less than 10 g cannot be detected in the dog even under optimum imaging conditions.[11]

Furthermore (1) activity in adjacent abdominal organs may obscure inferior infarcts; (2) a reduction in activity in the infarcted wall may be obscured by activity in the opposite wall, particularly in the presence of left ventricular hypertrophy; and (3) ^{201}Tl uptake may occur in islets of surviving myocardium within the region of myocardial scar.

By contrast, when ^{201}Tl scintigraphy is positive, the site of the perfusion defect accurately reflects the site of the myocardial infarct and often allows more precise delineation of its extent than does the electrocardiogram. ^{201}Tl scintigraphy examines the heart in several projections, allowing inspection of all regions of the left ventricle. However, the electrocardiographic localisation of infarction is influenced by the position of the heart, by regions of the left ventricle from which direct electrocardiographic recording is not possible (as in the case of posterior infarction), and by conduction defects which are common in the presence of old myocardial infarction.

The presence of a perfusion defect is related to the number of electrocardiographic leads showing Q waves, not to the type of QRS morphology. This is illustrated by the finding of perfusion defects in

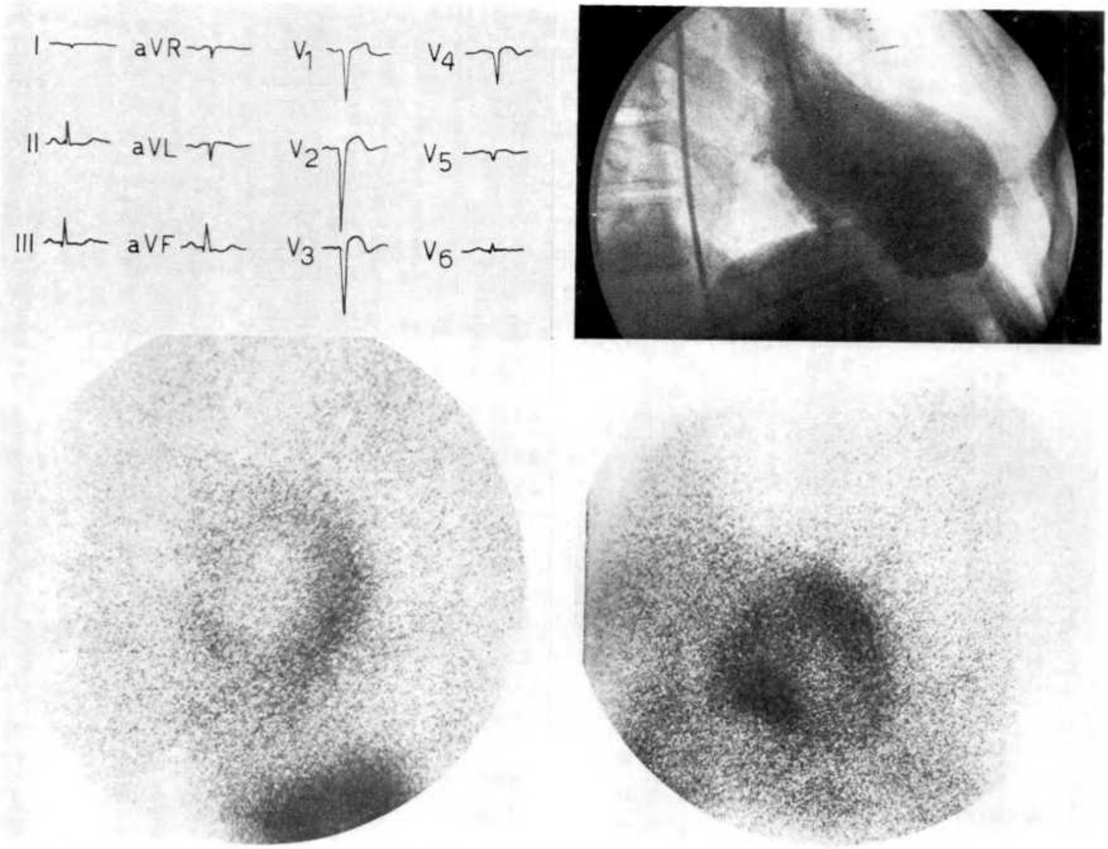

Fig. 3 *Electrocardiogram, ventriculogram (RAO, end-systole), and scintigrams of patient with electrocardiogram-defined, extensive, anterior infarction similar to that of Fig. 2. The LAO scintigram shows an anteroseptal and inferior perfusion defect. The AP projection shows an apical defect, extending into the inferior wall and corresponding exactly to the site of dyssynergy on the left ventriculogram. However, no evidence of inferior infarction is seen on the electrocardiogram. Coronary arteriography showed greater than 90 per cent proximal stenosis of both the left anterior descending and circumflex arteries with a normal right coronary artery.*

all extensive anterior infarcts and by the similar incidence of perfusion defects in regions with qR or QS patterns. The morphology of the QRS complex will obviously depend on the site of the exploring electrodes in relation to the site of the infarct. In a patient with qR complexes recorded in the classical praecordial lead positions, QS complexes may be recorded by changing the location of the recording electrodes. Inferior wall electrical activity is recorded by only three leads which are placed at a site remote from the infarct. Furthermore, the exact QRS morphology is time-dependent, thus qR complexes may be recorded at sites previously showing QS complexes. For the above reasons the QRS morphology does not indicate the extent of the infarct and, because of this, does not correlate with the presence or absence of ^{201}Tl perfusion defects.

The 74 per cent concurrence between the presence of Q waves and dyssynergy agrees with previous reports.[12] Of the regions showing discordance between electrocardiographic and ventriculographic abnormalities, two were posterior, a region difficult to evaluate by ventriculography,[13] and one was non-transmural; eight showed dyssynergy without Q waves or perfusion defect. These latter findings can be explained on the basis of a small scar, by interference with the synchronous contraction of the surrounding normal myocardium, producing disproportionately large ventriculographic abnormalities.[14] For this same reason, dyssynergy was less often related to perfusion

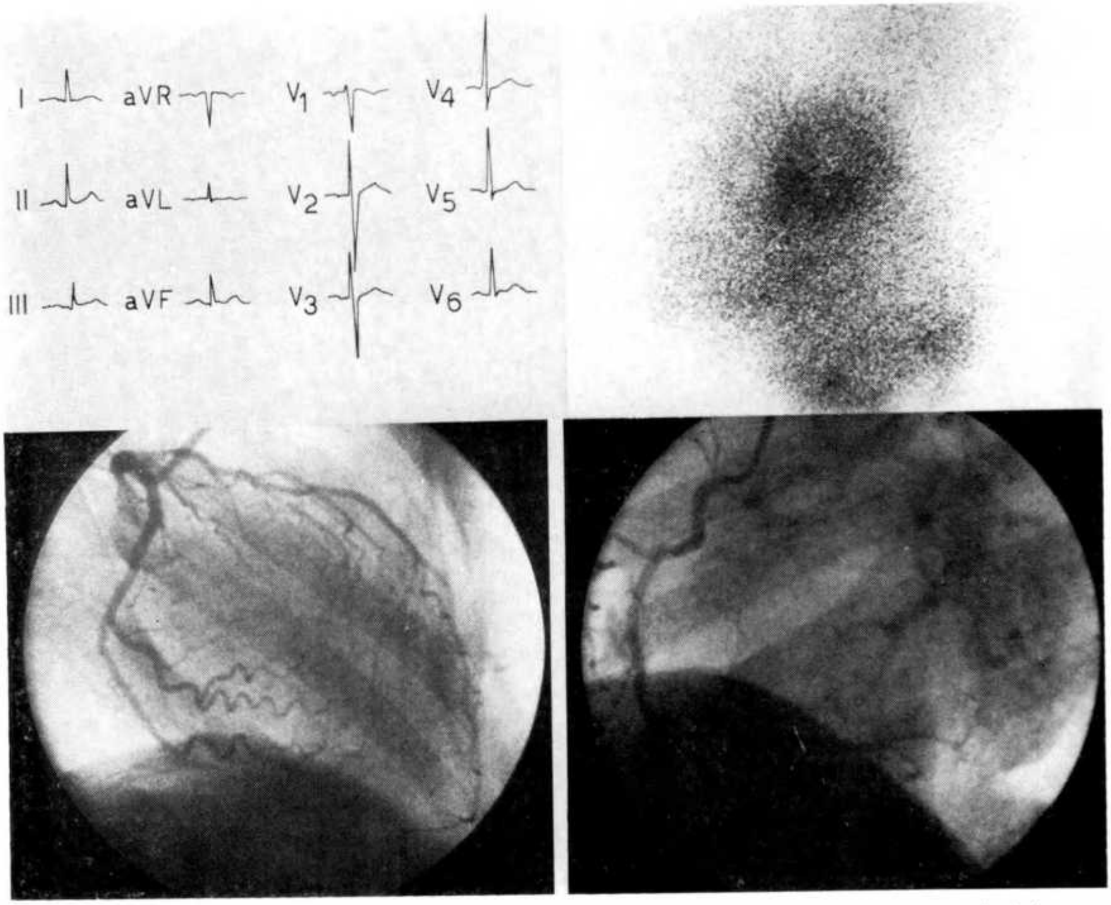

Fig. 4 *The presence of posterior infarction is more clearly demonstrated by the scintigram (LAO projection) than by the electrocardiogram. Furthermore, the infarcted region is supplied by normal coronary vessels, the only lesion being in the proximal part of the left anterior descending artery.*

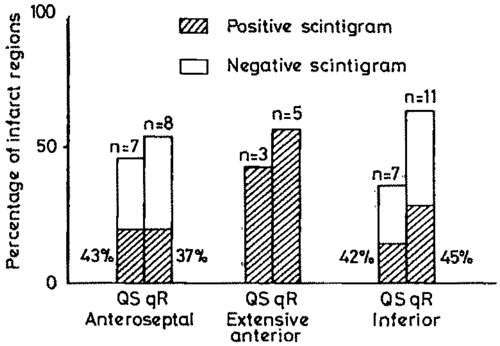

Fig. 5 *Relation of* ^{201}*Tl scintigraphic findings to QRS morphology in 41 regions of left ventricular infarction. On the ordinate is the percentage of regions of each infarct site (anteroseptal, extensive anterior, inferior) showing QS or qR complexes. For each infarct site and QRS morphology, the total number of regions and the percentage which are* ^{201}*Tl positive are given. Positive* ^{201}*Tl scintigrams are related to myocardial infarct extent, not to QRS morphology.*

defects than were Q waves, thallium scintigraphy being unable to detect small scars.

Other workers have found that old myocardial infarction is associated with severe coronary artery disease.[8, 15] Furthermore, Blood *et al.*[15] found resting ^{201}Tl perfusion defects in only 54 per cent of their patients. We also found positive resting ^{201}Tl scintigrams in 54 per cent (19) of our patients. However, in contrast to the findings of the above authors, we found that previous myocardial infarction was associated with a variable severity of coronary disease. Thirty-one per cent (six) of our patients with positive ^{201}Tl scintigrams had less than 90 per cent coronary obstruction and, conversely, 11 patients with infarction and negative resting ^{201}Tl scintigrams had greater than 90 per cent stenosis. It therefore appears that resting ^{201}Tl perfusion defects and infarction are not necessarily related to the severity of coronary artery disease. Severe coronary artery disease is not necessarily associated with myocardial infarction and the converse is also true.[16, 17] The reasons for this include the presence of collateral vessels,[18–20] and the possibility of functional changes[19, 21] in coronary vessels with a variable degree of atheromatous disease.

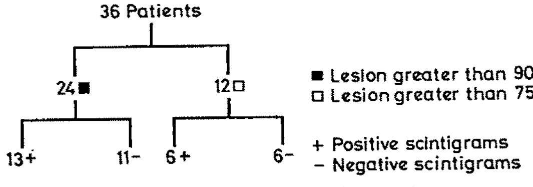

Fig. 6 *Relation of* ^{201}*Tl scintigraphic findings to the severity of coronary artery disease. The presence of a perfusion defect on* ^{201}*Tl scintigrams recorded at rest is independent of the severity of coronary artery disease in patients with old myocardial infarction.*

Conclusions

(1) When thallium scintigraphy is negative it does not rule out the presence of myocardial scar or abnormalities of wall motion.

(2) A resting thallium perfusion defect usually indicates the presence of moderate or severe infarction, with its associated abnormality of left ventricular function, and often localises and delineates the infarct with greater precision than the electrocardiogram.

(3) Regardless of whether thallium scintigraphy is positive or negative, it cannot be used to determine reliably either the site or the severity of coronary artery disease.

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Br Heart J 1980; **43**: 535–40

Diazepam in immediate post-myocardial infarct period

A double blind trial

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SUMMARY One hundred and thirty-one male patients admitted to a coronary care unit with myocardial infarction, later confirmed, were randomly allocated to receive either 10 mg diazepam every six hours, or a matched placebo, for 48 hours. During this period, no differences were found between the treatment groups in the incidence of fatal or non-fatal tachyarrhythmias even when account was taken of differences in the severity of the initial infarct. Monitored blood pressure and heart rate data were comparable as were the patients' self-assessed anxiety levels and symptoms, except that drowsiness was more common in the patients treated with diazepam.

Routine sedation of patients has been recommended for many years after coronary thombosis and indeed it has been suggested that patients are undersedated in the early post-infarct period.[1] Diazepam is a widely prescribed and safe drug which has been used in the management of the early convalescent phase of myocardial infarct.[2] *A priori*, it seems to be a desirable agent for four reasons.

Firstly, it should help the patient through an emotionally traumatic experience,[3] at the same time allowing him to rest more completely.

Secondly, a direct antiarrhythmic action has been attributed to the compound in animal experiments and in man.[4 5]

Thirdly, direct coronary artery vasodilatation by diazepam has been suggested.[6 7]

Fourthly, by relieving anxiety, there should be a reduction of circulating catecholamine levels and sympathetic autonomic discharge thus reducing the risk of arrhythmias being caused indirectly through these mechanisms.

A double blind controlled prophylactic trial of oral diazepam versus placebo was therefore carried out to determine whether an oral dose of 10 mg qds would reduce the incidence of death or of those tachyarrhythmias defined as requiring treatment.

Patients and methods

One hundred and seventy-two consecutive male patients with suspected myocardial infarction, and without arrhythmias on admission to the coronary care unit at Sheffield Royal Infirmary, were admitted to the trial. Patients too ill to take oral therapy or those having taken tranquillising drugs routinely over the previous month were excluded. Subsequent confirmation of the diagnosis of myocardial infarction depended upon: (1) the development of Q wave or T wave inversion in daily electrocardiograms; and (2) transient rise in the serum creatine kinase (CK) or aspartate transaminase (AST) above hospital normal values.

After random allocation (stratifying according to the time interval from the onset of pain) patients received either a white 10 mg tablet of diazepam or a placebo tablet matched for appearance. The first tablet was given on admission and treatment was then continued every six hours before meals for 48 hours when the trial terminated. Other treatment was given as clinically indicated over this time (see Table 6) but day-time sedation other than necessary analgesics or antiemetics was to be avoided.

Over the 48-hour period of assessment the following observations were recorded.

(1) MONITORING

Nursing staff took readings periodically and these were later summarised for each of the four 12-hour

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Received for publication 28 September 1979

periods by noting each type of arrhythmia and calculating the average of the following:

From central monitoring oscilloscope (readings lasting one minute in every 15 minutes)—frequency of ventricular extrasystoles and heart rate; and by auscultation (hourly)—lying systolic blood pressure, and lying diastolic blood pressure (stage 4 measurement).

(2) URINARY CATECHOLAMINES

Two 24-hour urine samples beginning on admission were analysed for each patient by a modification[8] of the method of Weil-Malherbe and Bone.[9]

(3) DAILY ELECTROCARDIOGRAM

The electrocardiogram and plasma urea, electrolytes, full blood counts, and ESR to detect patients with other serious disease were recorded, particularly renal abnormalities. (No such patients were encountered.)

(4) TRANSAMINASES (AST, CK, HBD)

Daily measurements were made, and for each patient the maximum value for each enzyme was used. CK was regarded as the best measure of initial infarct size.[10]

(5) PATIENTS' SELF-ASSESSMENT OF SYMPTOMS AND ANXIETY

Patients were asked on day 1 and again on day 2 to indicate by a cross on a continuous line their feelings about the opposites represented by the ends of the lines (see Table 6). For analysis the distance in inches of the cross from that end denoting mild (or no) symptom or anxiety was measured; this gave a score ranging from 0 to 6 inches (to the nearest tenth of an inch) corresponding to mild and severe symptoms, respectively. Two questions (Q10 relating to double vision and Q11 to pain in the fingers and toes) were used in combination to identify patients who were unlikely to report their symptoms reliably. Question 3 (chest pain) is a measure both of a physical symptom and of the patient's anxiety about it, and the two aspects are inextricably linked.

(6) DIAZEPAM AND ITS METABOLITES

Serum for diazepam and desmethyldiazepam, its active metabolite, was taken at the end of the first 24-hour period.

The size of the trial (60 to 70 patients per treatment group) was to be sufficiently sensitive to have a 50 per cent chance of detecting a halving of the real 48-hour incidence of tachyarrhythmias (assumed to be around 30%), if significance at the 5 per cent level is used; or an 80 per cent chance of detection at the same significance level if the real incidence in actively treated patients is reduced to one-third that of placebo treated patients.[11] "Real" in this context refers to large populations of patients of the designated type from which the trial samples are assumed to have been randomly selected.

Results

Of 172 patients admitted to the trial, 11 were subsequently excluded because they did not fulfil the entry criteria, and another 30 because neither the daily electrocardiograms nor the transaminase levels were confirmed; 131 valid participants remained. The treatment groups were comparable on admission in age, body weight, blood pressure, time from infarct to trial admission, Peel index,[12] site of infarct by electrocardiogram, proportion with heart failure, and past medical history (Table 1). The maximum of the three daily CK levels gave a higher mean for the diazepam patients (389 IU/l) than for those on placebo (319 IU/l), but this difference does not reach significance at

Table 1 *Comparability of treatment groups*

	Diazepam		*Placebo*	
On admission				
Mean age (y)	57	(67)	55	(63)
Age range (y)	37–80	(67)	36–69	(63)
Mean body weight (kg)	71	(58)	71	(53)
Mean systolic blood pressure (mmHg)	144	(62)	142	(58)
Mean diastolic blood pressure (mmHg)	92	(62)	90	(57)
Time from onset of attack to admission to trial (no. of patients)				
Less than 6 h	45	(68)	40	(63)
6-23h	18		16	
24–48 h or not known	5		7	
Peel index (mean ± SEM)	20·4 ±1·6	(60)	19·7 ±1·6	(55)
Max CK (IU/l) (of daily measurements over three days): mean ± SEM	389 ±29	(61)	319 ±23	(57)
Site of infarct (no. of patients): anterior	29	(61)	27	(55)
inferior	27		22	
other	5		6	
Heart failure clinically or radiologically (no. of patients)	19	(62)	22	(58)
Previous medical history (no. of patients):				
No. of previous infarcts: 0:	46	(62)	37	(58)
1:	11		13	
2+:	5		8	
Angina none:	26	(62)	23	(58)
for 2 weeks or less:	8		4	
for more than 2 weeks:	28		31	
Hypertension	3	(62)	9	(58)
Diabetes	2	(61)	2	(58)
No. of valid participants	68		63	

Note: Numbers of patients on which indices are based shown in parentheses; information not known for the remainder.

the 5 per cent level whether a normal or a lognormal distribution is assumed (Student's t test).

Similar numbers of patients in each treatment group died or were withdrawn from the trial during the 48 hours of trial treatment (Table 2).

Table 2 *Reasons for not completing 48-hour treatment*

	No. of patients on:	
	Diazepam	*Placebo*
Death (time in parentheses) after:		
Cardiogenic shock	—	2 (3,18 h)
Primary asystole	1 (4 h)	—
Ventricular fibrillation	—	1 (15 h)
Other reasons (time of event in parentheses):		
Early discharge	2 (17,25 h)	1 (40 h)
Cerebrovascular accident	—	1 (6 h)
Depressed respiration	1 (time unknown)	—
Total no. not completing treatment	4	5

ARRHYTHMIAS

The groups were also similar in the numbers of patients suffering arrhythmias in this period, and in the distribution of types of arrhythmia (Table 3). Arrhythmias tabulated are those for which treatment is customarily given; the ventricular extrasystoles were those of 6 beats per minute or more suggested by Lown *et al.*[13] as requiring treatment.

Table 3 *Tachyarrhythmias normally requiring treatment: patients validly completing 48-hour treatment*

*'Main' arrhythmia**	*No. of patients on:*	
	Diazepam	*Placebo*
Primary ventricular fibrillation	2	1
Ventricular tachycardia	6	7
Ventricular extrasystoles (6 beats/min or more)	8	2
Supraventricular tachycardia	6	8
Total no. of patients completing treatment but developing tachyarrhythmia(s)	22	18

* Where more than one type occurred, the patient is counted in the highest applicable row of the table.

In Table 4 the incidence of tachyarrhythmias is compared between the two treatment groups, stratifying according to two factors thought likely to influence this incidence, that is the maximum of the three daily values of CK and the time from infarction to admission to the trial. The diazepam group contained a higher proportion than the placebo group of patients with a maximum value of CK of 600 IU/l or more (who had a high risk of tachyarrhythmia). The data as laid out in this Table may be used to compare the incidence between the two treatment groups, taking account of the CK and time to admission, by means of Cochran's test,[14] and there is no significant difference (critical ratio = 0·27: $p > 0{\cdot}05$).

MONITORING

In Table 5, a summary of the monitoring data is given, excluding the four patients who died after only a few hours of monitoring (see Table 2). For brevity, heart rate and blood pressure data are summarised for the first 12 hours and for the last 12 hours of the 48-hour period of the trial.

Bearing in mind the sizes of the standard errors of the mean in Table 5 there are no remarkable contrasts, other than in the higher CK and aspartate transaminase levels in the diazepam group. Some of the catecholamine data are not available for analysis, for technical reasons or because there were doubts about the completeness of the "24-hour urine" sample from which they were obtained.

If Table 5 is subdivided (not shown) according to the maximum CK level attained, then among patients with maximum values in the range 0 to 299 IU/l, the mean systolic and mean diastolic blood pressures during the first 12 hours were each significantly higher* for 25 such diazepam patients (149/95 mmHg) than for the same number of controls (133/87 mmHg). However, further analysis shows that these figures simply reflect mean blood pressures on admission which were higher among these 25 diazepam patients.

SYMPTOMS AND ANXIETY LEVELS

For 53 patients on diazepam and 50 on placebo, suitable records of self-assessment of symptoms and anxiety were available (Table 6). Among the records excluded were those of three patients on diazepam who were too drowsy to complete them and those of three further patients (also on diazepam) who claimed double vision (Q10) *and* pain in their fingers and toes (Q11). As Table 6 shows, these two symptoms were unimportant (regardless of treatment group or day), as indicated by the small numbers of patients reporting them (five to 10) and the low median scores (0·7 to 1·3) among those few patients. Palpitation (Q2) was not common in either treatment group though when reported it was severe on day 1. Most symptoms were less common and/or less severe on day 2 than on day 1. Among the placebo patients, however, 10 more were preoccupied with their heart (Q4) on day 2 (42) than on day 1 (32), and among the diazepam patients it was the same number (31) on the two days. In each treatment group on each day over three-

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* Student's two-sample t tests: systolic BP: $t = 3{\cdot}14$, $df = 48$, $p < 0{\cdot}01$; diastolic BP: $t = 2{\cdot}69$, $df = 48$, $p < 0{\cdot}05$.

Table 4 *Incidence of tachyarrhythmias*

Risk factor	*Diazepam*			*Placebo*		
	Total	*Tachyarrhythmias (No.)*	*(%)*	*Total*	*Tachyarrhythmias (No.)*	*(%)*
(1) CK ≥600 IU/l and time from onset <6 h	4	2	50·0	3	1	33·3
(2) CK ≥600 IU/l and time from onset ≥6 h	7	6	85·7	1	—	—
(3) CK 300–599 IU/l and time from onset <6 h	18	8	44·4	18	7	38·9
(4) CK 300–599 IU/l and time from onset ≥6 h	7	3	42·9	6	1	16·7
(5) CK <300 IU/l and time from onset <6 h	14	3	21·4	17	7	41·2
(6) CK <300 IU/l and time from onset ≥6 h	11	—	—	10	2*	20·0
(7) Time from onset or CK value not known	7	—	—	8	1	12·5
Total	68	22	32·4	63	19*	30·2

* Includes one patient who died in ventricular fibrillation.

quarters of the patients were worried about what had happened (Q5), about a third admitted to being frightened (Q6), and about half were tense (Q7).

Chest pain (Q3) was reported on day 1 by half the placebo group and two-thirds of the diazepam group; on day 2 fewer patients reported the symptom and it was less severe, and for the diazepam group there were significantly more patients whose chest pain improved than whose pain deteriorated ($p < 0{\cdot}01$). In both treatment groups drowsiness (Q9) was reported by over two-thirds of patients on each day but was more severe in the diazepam patients: when the entire groups were compared by the Mann-Whitney test,[15] the distribution of drowsiness scores was significantly more severe in the diazepam group, both on day 1 ($p < 0{\cdot}05$) and even more so on day 2 ($p < 0{\cdot}001$). In the placebo group significantly more patients became less sleepy on day 2 than became more sleepy ($p < 0{\cdot}05$), and there was also a significant difference between the treatment groups in the distribution of patients among the three categories—"improved", "deteriorated", "unchanged" ($\chi^2_2 = 6{\cdot}03$: $p < 0{\cdot}05$), indicating less rapid recovery with diazepam.

OTHER FINDINGS

Serum levels of diazepam and of its active metabolite desmethyldiazepam were measured in a randomly selected subgroup of 24 of the patients on diazepam. The mean level of diazepam was 149 ng/ml and the mean level of desmethyldiazepam 88 ng/ml.

Although the trial procedure requested that sedatives should not be prescribed, about half the patients on diazepam and on placebo were given a sedative (Table 7), usually prochlorperazine, as an antiemetic, and/or nitrazepam at night. If anything,

Table 5 *Monitoring data: patients surviving 48 hours*

			Diazepam	*Placebo*
Peel index (mean ± SEM)			20·4 ± 1·6 (60)	19·5 ± 1·7 (54)
Transaminases (mean of max values in IU/l, ± SEM):		CK	389 ± 29 (61)	321 ± 23 (55)
		AST	246 ± 25 (61)	180 ± 18 (55)
		HBD	755 ± 53 (61)	685 ± 55 (55)
Urinary catecholamines (µg/24 h)				
Mean adrenaline ± SEM:	day 1		26·8 ± 2·7 (45)	31·2 ± 5·6 (43)
	day 2		22·5 ± 3·7 (45)	19·4 ± 3·1 (43)
Mean noradrenaline ± SEM:	day 1		98·7 ± 8·9 (48)	101·8 ± 10·8 (43)
	day 2		108·7 ± 8·8 (48)	119·3 ± 9·9 (43)
Heart rate (12 hourly means, beats/min, ± SEM):		0–12 h	80·0 ± 1·7 (61)	80·5 ± 2·1 (54)
		36–48 h	88·9 ± 2·9 (58)	82·1 ± 3·1 (53)
Blood pressure (12 hourly means, mmHg, ± SEM):	Systolic:	0–12 h	140·3 ± 3·6 (62)	134·1 ± 3·0 (55)
	Diastolic:	0–12 h	92·4 ± 1·7 (62)	89·3 ± 1·8 (55)
	Systolic:	36–48 h	125·6 ± 2·4 (59)	125·2 ± 2·5 (54)
	Diastolic:	36–48 h	81·9 ± 2·4 (57)	79·3 ± 2·3 (54)
Total no. of patients surviving 48 hours			67	60

SI units conversion factors for adrenaline 1 µg ≈ 0·0055 µmol; for noradrenaline 1 µg ≈ 0·0059 µmol.

Note: numbers of patients on which indices are based are shown in parentheses; data missing for remaining patients.

Table 6 *Self-rating symptom and anxiety scores*
For each symptom, scores range from 0·0 (mild) to 6·0 (severe)

Symptom, etc. (labelling of ends of line shown n parentheses)		*No. with scores ≥0·5, and, in parentheses, median scores for these patients*				*Patients improving* (scoring at least 0·5 less on day 2 than on day 1) *as proportion of all patients showing a change in either direction of at least 0·5*	
		Day 1		*Day 2*			
		Diazepam (n=53)	*Placebo (n=50)*	*Diazepam (n=53)*	*Placebo (n=50)*	*Diazepam*	*Placebo*
Q 1	Nausea and vomiting (vomited a good deal/ not nauseated)	20 (1·2)	18 (1·5)	8 (2·0)	11 (1·7)	15/20	12/18
Q 2	Palpitation (yes/no)	7 (3·6)	13 (3·2)	6 (1·2)	10 (1·0)	4/7	8/13
Q 3	Chest pain (severe/none)	34 (2·0)	24 (2·1)	26 (1·5)	19 (1·8)	25/32§	16/23
Q 4	Think about heart (most of time/never)	31 (2·8)	32 (2·7)	31 (2·8)	42 (2·3)	18/32	16/34
Q 5	Worried about what has happened (very/not bothered at all)	46 (2·9)	45 (3·6)	42 (2·9)	42 (3·2)	20/37	19/31
Q 6	Frightened (very/not at all)	21 (2·0)	21 (1·6)	18 (1·6)	14 (1·9)	13/21	14/20
Q 7	Tension (tense/relaxed)	29 (2·3)	23 (1·8)	29 (1·6)	25 (1·8)	18/30	12/25
Q 8	Irritability (easily irritated/completely calm)	25 (2·8)	26 (1·5)	21 (1·9)	18 (1·0)	13/19	19/24‡
Q 9	Drowsiness (wide awake/sleepy)	42 (5·4)*	37 (3·8)	42 (5·2)†	34 (2·7)	15/31‖	26/36‡
Q10	See two of everything (yes/no)	5 (0·9)	6 (0·9)	7 (0·7)	6 (0·8)	2/5	4/6
Q11	Pain in fingers and toes (yes/no)	6 (1·3)	10 (1·2)	5 (1·0)	5 (0·7)	5/7	7/9

Mann-Whitney U test (Siegel[15], p 116 ff) for comparison of *entire* diazepam group with the *entire* placebo group on same day: *, $p < 0·05$. †, $p < 0·001$.

Sign test (Siegel[15], p 68 ff) for comparison *within one treatment group only* of observed proportion against an 'expected' proportion of 0·5: ‡, $p < 0·05$. §, $p < 0·01$.

χ^2 test for comparison of numbers of diazepam patients in 'improved', 'deteriorated', 'unchanged' categories with corresponding number of placebo patients: ‖, $\chi^2_2 = 6·03$, $p < 0·05$.

a higher proportion of patients on diazepam took these sedatives as well as dihydrocodeine which has sedative properties. The proportions of patients requiring any analgesics and those requiring any drugs to treat heart failure were each comparable between the two treatment groups. However, diuretics (mainly bendrofluazide and frusemide) were taken by a higher proportion of those on placebo than of those on diazepam.

Discussion

Melsom *et al.*[16] claimed that "obvious signs of unrest and anxiety" and the need for analgesia were reduced by diazepam in the immediate post-infarct period. Their trial, however, was not reported as double blind and the numbers were smaller than in the present study. We have obtained subjectively scored symptoms and anxiety levels of patients, including those specifically related to their myocardial infarction. Sedation occurred more frequently in those on diazepam than in those on placebo, but anxiety levels as such were comparable in the two groups throughout.

Slightly higher proportions of the patients on diazepam than of the controls were given other drugs which have sedative action. Whatever the cause of sedation, we have been unable to demonstrate that diazepam is more effective than placebo in relieving the patient's anxiety or awareness of pain. In assessing a patient's level of anxiety, observers may be misled into assuming that a drowsy patient is not an anxious one, a conclusion that is not supported by these results. It is, however, possible that sedation may blunt subsequent memory of the events though we have not attempted to assess this in the present study. It is common to draw a distinction between the somatic and psychological components of anxiety. In the circumstances of this study anxiety may have been somatic in

Table 7 *Associated drug treatment*

	No. of patients on:	
	Diazepam	*Placebo*
Drug records mislaid	6	5
Analgesics		
Dihydrocodeine	38	30
Diamorphine	40	35
Any drug*	53	46
Sedatives		
Nitrazepam	11	4
Prochlorperazine	29	22
Any drug*	37	24
Antiarrhythmic agents		
Lignocaine	11	5
Any drug*	17	11
Drugs used to treat heart failure		
Diuretics	22	33
Digoxin	6	8
Any drug*	26	35
Other drugs	10	8
Total no. of patients	68	63

* Including those listed.

origin and therefore less accessible to a central psychotropic action.

There was a suggestion from the maximum CK and AST levels attained that the two groups may not have been comparable in the severity of their infarcts on admission to the trial, but corrections were made for this in the analysis.

Other monitored data including heart rate, blood pressure, and tachyarrhythmias showed no consistent differences (though the one minute in 15 sampling procedure is likely to underestimate the number of tachyarrhythmias, to the same extent in each treatment group, in contrast to the semi-automated analysis of continuous recordings for which equipment is now commercially available). On the whole, therefore, the treatment groups were similar in the monitored physiological and biochemical data.

The important difference between this study and that of Melsom *et al.*,[16] apart from the use of double-blind controls, is that they used an intravenous loading dose of diazepam, while we did not. It is difficult to compare serum levels of diazepam and of its active metabolite between the studies since they took repeated blood samples over 72 hours (finding accumulation over this time), whereas in this study serum was taken at the end of the first 24-hour period only for a random sample of 24 patients.

Thus, apart from the possibility that diazepam could be responsible for small increases in CK levels, we did not observe any major unwanted side effects. However, it seems unlikely that any major beneficial effect other than sedation accrues from the use of diazepam in the post-myocardial infarction state. In particular, the half to two-thirds reduction in the incidence of tachyarrhythmias which the trial was capable of detecting was not found.

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Br Heart J 1980; **43**: 541–5

Echocardiographic comparison of haemodynamic effects of metoprolol and propranolol

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SUMMARY Metoprolol (200 mg daily) and propranolol (160 mg daily) were each given for one week to 11 normal subjects. The order of administration was randomised and not known to us during the study. Each period of treatment with active drug was followed by one week during which placebo tablets were taken.

M-mode echocardiograms and blood pressure were recorded before entry to the trial, twice during each week of treatment with metoprolol or propranolol, and daily for three days and on the seventh day after stopping the drugs. Septal and posterior wall endocardial echoes were traced with an X-Y digitiser and left ventricular minor axis dimensions derived every 10 ms with a minicomputer.

Both drugs reduced heart rate, cardiac output, and blood pressure. Systemic vascular resistance was increased significantly by propranolol, and with both agents was inversely related to heart rate, cardiac output, left ventricular diastolic dimension, and indices of contractility.

Beta-adrenergic blocking agents have measurable effects on haemodynamic, angiocardiographic, and echocardiographic indices of left ventricular function. We have used echocardiography to make repeated measurements of left ventricular dimensions and contractility and of cardiac output and systemic vascular resistance during a crossover trial of metoprolol and propranolol, and compared the effects of these agents and their duration after stopping each drug.

Methods

The subjects were normal volunteers who gave their informed consent. They were between 21 and 29 years of age, and were selected because we were able to record left ventricular echocardiograms of high quality. After baseline studies each subject took either propranolol (80 mg bd orally) or metoprolol (100 mg bd orally) for one week (weeks 1 and 3). The order of administration was randomised and matching placebo was used throughout. During weeks 2 and 4 placebo only was given. The drugs were packaged in Dosetts, a weekly tablet dispensing system. The procedure is summarised in Fig. 1.

Echocardiograms were recorded before admission to the trial, twice during each phase of active drug administration, and daily for three days and on the seventh day after the drugs were stopped. Blood pressure was recorded by sphygmomanometry at each visit and a blood sample was taken for estimation of plasma level of active drug[1] at the end of the first and third weeks.

Standard left ventricular echocardiograms were recorded with the subjects lying supine or rolled towards the left, using an Ekoline 20 A echocardio-

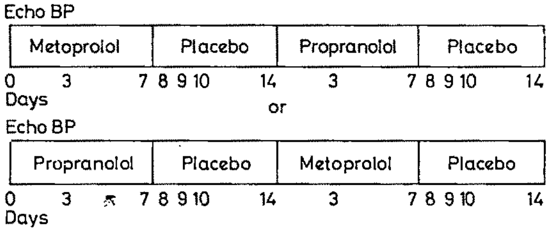

Fig. 1 *Study procedure. Each subject was studied for four weeks. Active drugs were taken during the first and third weeks. Recordings of left ventricular dimensions (echo) and blood pressure (BP) were made at the beginning of the study (day 0), twice during each period of beta-adrenergic blockade (days 3, 7), daily for the first three days of each placebo phase (days 8, 9, 10), and on day 14. Blood samples were taken for plasma levels of metoprolol and propranolol on day 7 of the first and third weeks.*

Received for publication 8 March 1979

graph, Electronics for Medicine VR6 recorder, and 2·25 or 3·5 MHz focused transducers, at a paper speed of 50 mm/s. Depth calibrations were checked against a standard test object, and time markers against a 50 Hz mains signal.

When the records were of sufficiently good quality the left ventricular septal and posterior wall endocardial echoes were traced with the cursor of an X-Y digitiser (Hewlett-Packard 9864A) through at least five cycles. Depth calibrations during the portion of the recording to be digitised, time markers (1 s), and onset of QRS were entered. Corrections were made for alignment of the recording on the digitising table, and for nonlinearity of the 1 cm depth calibrations. The data were analysed with a Hewlett Packard 9825A minicomputer with 23228 bytes of internal memory. Linear interpolation was used to derive ventricular dimensions at 10 ms intervals. A five-point running filter was used to reduce sampling jitter.

Dd (dimension at onset of QRS) and Ds (dimension at peak posterior wall excursion) were calculated and stored. The instantaneous gradients of ventricular dimension (dD/dt) were calculated and 'normalised' for the average minor axis diameter ([Dd + Ds]/2). The gradient at a particular time was taken as the average of that during three preceding and following 10 ms intervals. The maximum systolic and diastolic gradients were stored (Fig. 2). When six or more cycles were digitised the computer calculated the mean and SD for each variable and rejected the value with the largest deviation. This was repeated until only five cycles were left. When the septal and posterior wall endocardium were not defined completely Dd, Ds, and R-R interval were measured for five cycles.

Stroke volume (SV) and cardiac output ($\dot{Q}s$) were derived using cubed systolic and diastolic dimensions (eg $SV = [Dd]^3 - [Ds]^3$) and using the formula of Teichholz *et al.*[2] Systemic resistance (Rs) was calculated assuming $BP_{mean} = (BP_{[d]} + [BP_{[s]} - [BP_{[d]}]/3)$ mmHg and right atrial mean pressure 0 mmHg.

Fractional shortening (FS) was derived from the formula $FS = ([Dd - Ds]/Dd) \times 100$, and mean velocity of circumferential shortening (Vcf) from $Vcf = [Dd - Ds]/[Dd \times ET]$ where ejection time (ET) was the interval from onset of QRS to peak posterior wall excursion–50 ms.

Statistical comparisons were made using Wilcoxon's signed rank test and Student's paired t test.

Results

Eleven subjects (six men, five women) were studied. None withdrew because of adverse reactions to either drug, and the only effect noted was undue fatigue during extremes of exertion such as playing squash. Mean values for the data are summarised in the Table. Baseline values (day 0) and those on days 14 and 28 did not differ significantly from those recorded on other normal adults in the same age range (men: Dd 50 ± 3 mm, Ds 34 ± 4 mm, systolic dD/dt_{max} 2·2 ± 0·4 diam/s, diastolic dD/dt_{max} 2·3 ± 0·6 diam/s; women: dD 43 ± 3 mm, Ds 28 ± 3 mm, systolic dD/dt_{max} 2·5 ± 0·4 diam/s, diastolic dD/dt_{max} 3·2 ± 0·7 diam/s.

Both drugs produced significant reductions in heart rate, mean blood pressure, and cardiac output. With propranolol the heart rate and blood pressure reductions were still significant the day after the drug was stopped. Propranolol administration resulted in reduction in left ventricular diastolic dimension and diastolic dD/dt_{max}, and with an increase in the systemic vascular resistance (Table). When the drugs were compared, mean values for diastolic dimension and cardiac output were greater with metoprolol, while diastolic dD/dt_{max}, mean blood pressure, and peripheral resistance were less.

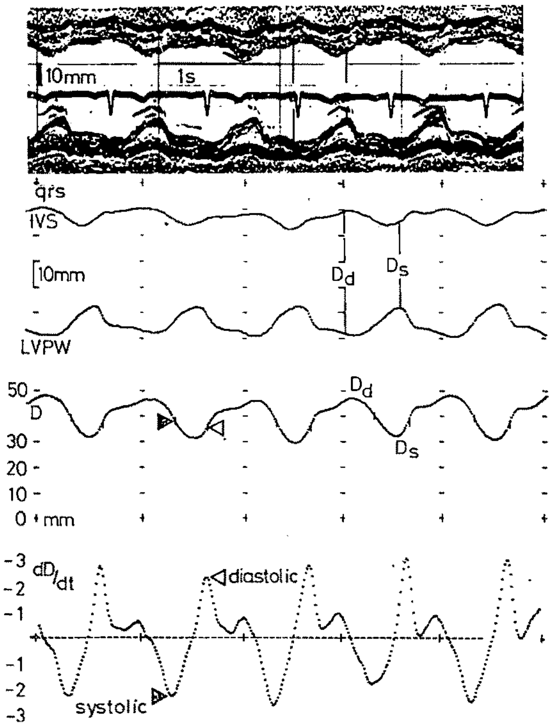

Fig. 2 *Analysis of echocardiograms. A standard M-mode left ventricular echocardiogram is shown, with plots of septal (IVS) and posterior wall (LVPW) endocardium, instantaneous dimension (D), and "normalised" rate of change of dimension (dD/dt).*

For both drugs there were significant negative correlations between peripheral vascular resistance and diastolic dimension ($r = 0{\cdot}67$, $p < 0{\cdot}001$), mean Vcf ($r = 0{\cdot}42$, $p < 0{\cdot}05$ [propranolol]; $r = 0{\cdot}53$, $p < 0{\cdot}01$ [metoprolol]), fractional shortening ($r = 0{\cdot}59$ [propranolol] and 0·49 [metoprolol], $p < 0{\cdot}001$), systolic ($r = 0{\cdot}48$, $p < 0{\cdot}001$ [propranolol], $r = 0{\cdot}32$, $p < 0{\cdot}01$ [metoprolol]) and diastolic ($r = 0{\cdot}41$ [propranolol[and 0·42 [metoprolol], $p < 0{\cdot}001$) dD/dt_{max}, heart rate ($r = 0{\cdot}35$, $p < 0{\cdot}01$ [propranolol], $r = 0{\cdot}42$, $p < 0{\cdot}001$ [metoprolol]), and cardiac output ($r = 0{\cdot}87$, $p < 0{\cdot}001$).

Plasma levels of metoprolol (0·76 ± 0·46, range 0·37 to 1·72 µmol/l) and propranolol (0·26 ± 0·22, range 0·03 to 0·66 µmol/l) on day 7 of the adminis-tion of the active drug could not be correlated with changes from baseline values in heart rate, left ventricular dimensions, fractional shortening, blood pressure, cardiac output, or peripheral vascular resistance.

Discussion

Standardised echocardiographic methods[3] have been used to determine left ventricular function in patients with heart disease[4 5] and in subjects undergoing physical training,[6] and during the administration of drugs.[7–9] Comparisons with angiocardiography have confirmed the validity of the echocardiographic measurement of left ventricular dimensions and volumes,[10–12] and of mean[13 14] and peak[15] rates of change of dimension. The expression of left ventricular volumes as cubed minor axis dimensions[11] has been shown to be inaccurate in patients with ventricular dilatation or dyskinesia.[2] We calculated volumes by cubing dimensions and by the formula of Teichholz *et al.*,[2] and as might be expected we found that there was excellent correlation between these methods in our young healthy subjects ($r = 0{\cdot}98$, $p < 0{\cdot}001$). There was also good correlation ($p < 0{\cdot}001$) between the

Table *Mean values for diastolic (Dd) and systolic (Ds) minor axis dimensions, fractional shortening (FS), peak rates of change of ventricular dimensions (dD/dt_{max}), heart rate (HR), mean blood pressure (BP), cardiac output ($\dot{Q}_S$), and systemic vascular resistance (R_S)*

	Dd *(mm)*	*Ds* *(mm)*	*FS* (%)	*dD/dt max* *(diastolic)* *(circ/s)*	*dD/dt max* *(systolic)* *(circ/s)*	*HR* *(beats/min)*	*Mean BP* *(mmHg)*	$\dot{Q}_S$ *(l/min)*	R_S *(units)*
Day 0	48 ±3 (n=11)	32 ±1 (n=11)	34 ±3 (n=11)	3·0 ±0·6 (n=11)	2·2 ±0·3 (n=11)	68 ±10 (n=11)	90 ±6 (n=9)	5·4 ±1·2 (n=11)	16 ±4 (n=9)
Metoprolol									
Day 3	48 ±3 (n=11)	31 ±3 (n=11)	35 ±4 (n=11)	2·7 ±0·6 (n=11)	2·3 ±0·5 (n=11)	60 ±11* (n=11)	82 ±6 (n=11)	4·7 ±0·9* (n=11)	18 ±3 (n=11)
Day 7	48 ±3 (n=10)	32 ±3 (n=10)	34 ±6 (n=10)	2·7 ±0·5 (n=10)	2·1 ±0·4 (n=10)	58 ±9** (n=10)	79 ±5* (n=10)	4·4 ±1·0** (n=10)	19 ±5 (n=10)
After stopping metoprolol									
Day 8	47 ±3 (n=11)	30 ±3 (n=11)	36 ±5 (n=11)	2·7 ±0·5 (n=9)	2·2 ±0·3 (n=9)	64 ±9 (n=11)	78 ±7** (n=11)	4·9 ±1·1 (n=11)	17 ±5 (n=11)
Day 9	49 ±4 (n=11)	31 ±3 (n=11)	36 ±5 (n=11)	2·9 ±0·7 (n=11)	2·4 ±0·4 (n=11)	67 ±9 (n=11)	86 ±10 (n=11)	5·7 ±1·2 (n=11)	16 ±3 (n=10)
Day 10	48 ±3 (n=11)	31 ±3 (n=11)	35 ±4 (n=11)	2·8 ±0·8 (n=10)	2·4 ±0·3 (n=10)	72 ±10 (n=11)	88 ±5 (n=11)	5·9 ±1·9 (n=11)	16 ±5 (n=11)
Day 14	47 ±4 (n=11)	32 ±3 (n=11)	33 ±5 (n=11)	2·6 ±0·6 (n=11)	2·2 ±0·3 (n=11)	71 ±12 (n=11)	89 ±7 (n=11)	5·5 ±1·8 (n=11)	18 ±6 (n=11)
Propranolol									
Day 3	46 ±4*† (n=11)	31 ±2 (n=11)	34 ±4 (n=11)	2·6 ±0·7* (n=9)	2·1 ±0·3 (n=9)	55 ±7** (n=11)	82 ±6** (n=11)	3·9 ±1·3**† (n=11)	23 ±8*† (n=11)
Day 7	47 ±3 (n=11)	30 ±2 (n=11)	35 ±5 (n=11)	3·0 ±0·6† (n=10)	2·4 ±0·4 (n=10)	56 ±4** (n=11)	81 ±6* (n=11)	4·3 ±1·1** (n=11)	20 ±7 (n=11)
After stopping propranolol									
Day 8	48 ±4 (n=10)	31 ±2 (n=10)	35 ±5 (n=10)	2·7 ±1·0 (n=10)	2·3 ±0·4 (n=10)	60 ±9** (n=10)	82 ±7*† (n=10)	4·7 ±1·1 (n=10)	19 ±5 (n=10)
Day 9	47 ±3 (n=11)	31 ±2 (n ±11)	35 ±5 (n=11)	3·2 ±0·5 (n=9)	2·5 ±0·3 (n=9)	68 ±10 (n=11)	82 ±9 (n=11)	5·0 ±1·0 (n=11)	17 ±5 (n=10)
Day 10	47 ±2 (n=11)	30 ±2 (n=11)	35 ±4 (n=11)	3·0 ±0·8 (n=11)	2·4 ±0·4 (n=11)	70 ±11 (n=11)	86 ±9 (n=11)	5·2 ±1·2 (n=11)	17 ±4 (n=11)
Day 14	48 ±4 (n=10)	32 ±3 (n=10)	34 ±4 (n=10)	3·0 ±0·6 (n=9)	2·3 ±0·3 (n=9)	69 ±11 (n=10)	83 ±9 (n=10)	5·1 ±1·2 (n=10)	17 ±4 (n=10)

Significant differences (Wilcoxon's signed rank test) from baseline values (day 0) are indicated by * ($p < 0{\cdot}05$) and ** ($p < 0{\cdot}01$). Values during the administration of propranolol which differed significantly from those on the corresponding days on metoprolol are shown thus † ($p < 0{\cdot}05$). In general, analysis using Student's t test gave similar or higher levels of significance, except for increases in peripheral resistance on day 3 of propranolol administration compared with values on day 0 ($z = 2{\cdot}19$*; $t = 2{\cdot}27$).

different indices of contractility (FS vs dD/dt_{max}, $r=0{\cdot}75$; mean Vcf vs dD/dt_{max}, $r=0{\cdot}85$; FS vs mean Vcf, $r=0{\cdot}84$) suggesting that they are all of value in describing left ventricular systolic function.

Our normal values for systolic and diastolic dD/dt_{max} were similar to those reported by Gibson and Brown,[15] and Paoloni *et al.*[16] and were not affected materially by smoothing and averaging during computer analysis. We compared recordings made at 50 mm/s and at 100 mm/s using as a model two sine waves with a 90° phase difference, and found no significant differences in the derived "dimensions" and rates of change of "wall motion". We were concerned about differences from cycle to cycle and from day to day, and particularly about the fairly large variations in peak rates of change of dimension noted by Bass and Whitlock.[17] In other studies we have analysed up to 50 successive cycles in normal subjects with sinus arrhythmia, and found that dimensions varied by as much as 10 per cent and peak rates of change by up to 25 per cent. For this reason we measured at least five cycles and used only recordings of high quality for calculating rates of change of dimension.

It seems to us that this difficulty in obtaining representative measurements of ventricular dimensions and wall motion must apply also to angiocardiographic techniques. There is no information on the beat-to-beat variation which may occur in radiological studies. Echocardiography had the great advantage of allowing us to obtain a much larger sample on any one occasion and to obtain repeated measurements under comparable conditions. Fig. 3 illustrates the variation in ventricular dimensions and in derived stroke volume and "instantaneous" cardiac output in 92 consecutive cycles in one of our subjects.

Although other authors have suggested that the does of metoprolol and propranolol we chose are comparable in effect,[18–20] we found that there was a tendency for propranolol to produce greater falls in heart rate and cardiac output, and significant increases in the systemic vascular resistance. There is a fairly large scatter in the values for cardiac output and systemic resistance which could have been reduced if these had been "corrected" for body surface area, but as the subjects were compared with themselves the levels of significance would not have been altered. Fig. 4 shows the changes observed.

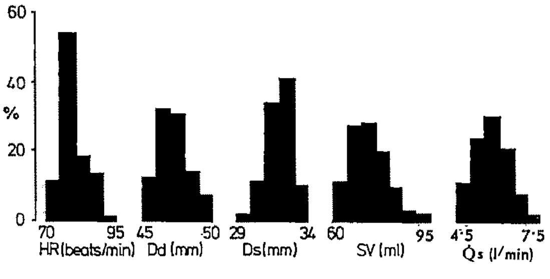

Fig. 3 *Frequency plots of heart rate, left ventricular dimensions (Dd, Ds), stroke volume (SV), and "instantaneous" cardiac output ($\dot{Q}s$) in 92 successive cardiac cycles in one normal subject.*

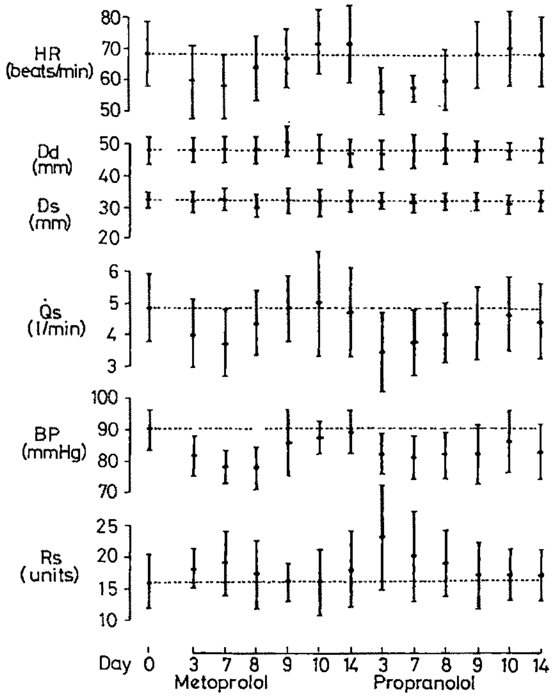

Fig. 4 *Heart rate (HR), ventricular dimensions (Dd and Ds), cardiac output ($\dot{Q}s$), mean blood pressure (BP), and systemic resistance (R_S) during metoprolol and propranolol treatment (days 3, 7), and after stopping each drug (days 8, 9, 10, 14). The data have been plotted as if all the metoprolol studies were done first. The dotted lines represent mean values for control measurements.*

Van Herwaarden *et al.*[20] studied subjects after four weeks on metoprolol or propranolol and were able to show that the infusion of adrenaline increased forearm vascular resistance during propranolol treatment, but not during metoprolol treatment; this was found also in acute studies by Johnsson.[21] This seems to indicate an important difference in the properties of the two drugs which may have clinical relevance.

Crawford *et al.*[8] showed that propranolol reduced left ventricular ejection fraction and mean Vcf as well as heart rate and blood pressure, and that these effects could be reversed with atropine and phenylephrine. We were not able to show that either drug produced any significant change in indices of left ventricular systolic function (fractional shortening, peak Vcf, or systolic dD/dt_{max}), though the negative correlation between these indices and systemic vascular resistance suggests either that they are responsive to changes in afterload or that (like heart rate) they are directly affected by beta-adrenergic blocking agents. In any case the net effect is reduction in blood pressure resulting from a fall in cardiac output which is itself largely rate dependent.

Although it would be difficult to show that metoprolol should be preferred to propranolol in clinical practice, except for patients with asthma, the different effects of these and other beta-adrenergic blocking agents on peripheral vascular resistance at rest or during exercise or the infusion of catecholamines deserve further investigation. Despite its limitations M-mode echocardiography is a most attractive tool for studies of this kind.

We are grateful to Dr P Stanley, Queen Elizabeth Hospital, Adelaide, whose laboratory performed the assays of metoprolol and propranolol, and to Astra Pharmacuticals Pty Ltd and ICI Australia Ltd for supplies of active and matching placebo tablets.

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Br Heart J 1980; **43:** 546-9

Dilatation of coronary artery stenoses after isosorbide dinitrate in man*

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SUMMARY The effect of isosorbide dinitrate (ISDN), 5 mg sublingually, on the diameters of coronary artery stenoses (n=27) was examined in 20 patients. Another 18 patients with angiographically normal coronary arteries received the same amount of ISDN and were used as controls. Prestenotic and stenotic diameters were measured with a vernier calliper having an accuracy of 0·05 mm. The degree of stenosis was expressed as percentage of cross-sectional area reduction. ISDN caused uniform dilatation of every normal epicardial artery; mean increase in diameter was 21 per cent (range: 17 to 26%). In 18 stenoses (28 to 95% obstruction) there was very little change after ISDN. The mean prestenotic diameter increased from 2·82±0·48 mm to 3·05±0·43 mm and the mean stenotic diameter from 1·45±0·49 mm to 1·59±0·51 mm. However, in the nine other stenoses (35 to 89% obstruction) the mean degree of obstruction decreased significantly from 68±15·6 per cent to 47±15·6 per cent after ISDN. This improvement was a result of a significant increase of the mean stenotic diameter from 1·71±0·47 mm to 2·41±0·55 mm, whereas the prestenotic diameter showed only an insignificant increase from 3·17±0·63 mm to 3·31±0·58 mm after ISDN. In four patients with two obstructions in different coronary branches ISDN dilated one without significantly affecting the other lesion. From these data we conclude that ISDN can dilate some coronary artery stenoses but that this response may vary from one site to another even in the same patient.

Administration of nitrates constitutes one of the more important treatments for the relief of angina. The beneficial effect is dually attributed to the reduction of left ventricular preload by venous pooling and afterload by reducing systemic blood pressure.[1 2] The combination of these effects results in a decrease in left ventricular volume and wall tension, hence lower myocardial oxygen demand. However, from numerous studies[3–6] we have also learned that in man, nitrates dilate epicardial coronary arteries. Since any increase of luminal area in an obstructed coronary artery segment should improve blood flow substantially,[7 8] some of the therapeutic effects of nitrates may be attributable to dilatation of coronary artery stenoses.

Using a recently developed morphometric method for the exact measurements of coronary artery diameters,[9 10] this study examines the influence of sublingually administered isosorbide dinitrate (Isordil†) on the diameter of coronary arteries, with particular emphasis directed towards its effect on coronary artery stenoses.

Method

Two different groups of patients were entered in the study. The first group is composed of 18 patients evaluated for chest pain and in whom normal coronary arteries were found at angiography. The second group included 20 consecutive patients in whom clearly defined stenoses in one or more of the three major coronary branches were readily recognised in at least two different projections on angiography. In both groups the coronary angiogram was repeated five minutes after administration of 5 mg isosorbide dinitrate sublingually. In both the initial and the repeat coronary angiogram, coronary artery diameters were measured at the same sites from the screen of a Tagarno projector using a

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* This work was supported by the National Heart, Lung and Blood Institute (Program Project grant and SCOR on Ischemic Heart Disease). Dr Rafflenbeul is the recipient of a research grant of the Deutsche Forschungsgemeinschaft, Federal Republic of Germany.

Received for publication 18 August 1979

† Isordil was supplied by Ives Laboratories, New York

vernier calliper as described previously.[10] The enlargement factor caused by the image magnifier and the projection was approximately threefold and was determined exactly by comparison with the measurement of the catheter tip placed in the coronary ostium.

In angiographically normal coronary arteries only the arteries running nearly parallel to the image plane were measured in the different projections. Thus, we assessed the left anterior descending artery in the right anterior oblique projection, whereas the left circumflex and the main trunk of the right coronary artery were measured in the left anterior oblique projection. To minimise errors from pincushion distortion which can average as much as 7 per cent, the measurements were consistently performed near the central *x*-ray beam. Though we were unable to find any change in lumen diameter during the cardiac cycle, we always measured at end-diastole in order to eliminate blurring effect from rapid heart movements as well as errors caused by axial or spatial rotations.

In coronary arteries with obstructions, measurements were obtained from the prestenotic segment (5 to 10 mm before the stenosis) and from the narrowest portion of the obstruction. Taking into account the eccentric lumen of many obstructions, coronary lesions were measured in at least two different projections before and after isosorbide dinitrate. The degree of each stenosis was calculated by the formula:

$$\text{Per cent area stenosis} = 1 - \frac{D_{\text{sten}}^2}{D_{\text{norm}}^2} \times 100$$

In this formula D_{norm} is the diameter of the angiographically normal prestenotic vessel segment and D_{sten} the average stenotic diameter calculated as arithmetic mean of the measured stenotic diameters in different projections. This calculation uses the formula of the surface area of a circle ($A = \pi r^2$) to determine the respective cross-sectional area. Validation of this method has been established previously.[10]

To minimise observer bias and variability all angiograms were assessed by the same observer in a random sequence. Results are expressed as mean ±1 standard deviation (SD). The significance of a difference was assessed by the two-tailed paired Student's t test and a p value of $< 0·05$ was regarded as statistically significant.[11]

Results

Table 1 illustrates the diameter changes of normal coronary arteries after administration of 5 mg isosorbide dinitrate. The portion of the left anterior descending artery from its origin to the apex of the heart and the portion of the right coronary artery from its aortic orifice to the crux cordis were arbitrarily subdivided into a proximal, middle, and distal third. The left circumflex artery between its origin and the most distal obtuse marginal branch was divided into a proximal and a distal half. We compared measurements before and after administration of the nitrates, and in all these segments of normal coronary arteries there was a uniform and significant increase of vessel diameter. After isosorbide dinitrate the calibre of enlargements ranged from 17 to 26 per cent.

Table 2 summarises the results obtained before and after administration of isosorbide dinitrate to patients with coronary artery stenoses. A total of 27 obstructions, 10 in the left anterior descending artery, four in the left circumflex artery, and 13 in the right coronary artery were examined. In 16 patients with 18 stenoses, ranging from 28 to 95 per

Table 1 *Effect of isosorbide dinitrate 5 mg sublingually on the diameters (mm) of normal coronary arteries*

Coronary artery segment	*Before*	*Isosorbide dinitrate*	*After*
LAD			
Proximal	3·0 ±0·11		3·5 ±0·13*
Middle	2·5 ±0·08		3·0 ±0·10*
Distal	1·6 ±0·12		2·0 ±0·12*
LCX			
Proximal	2·7 ±0·10		3·4 ±0·10*
Distal	2·4 ±0·09		2·9 ±0·11*
RCA			
Proximal	3·2 ±0·12		3·8 ±0·13*
Middle	2·9 ±0·11		3·5 ±0·12*
Distal	2·6 ±0·11		3·1 ±0·13*

*p < 0·05. LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Table 2 *Effect of isosorbide dinitrate 5 mg sublingually on coronary artery stenoses*

	Before	*Isosorbide dinitrate*	*After*
Group A (n = 18)			
Degree of stenosis (% area)	70 ±17·3%		69 ±17·5%†
Prestenotic diameter (mm)	2·82 ±0·48		3·05 ±0·43†
Stenotic diameter (mm)	1·45 ±0·49		1·59 ±0·51†
Group B (n = 9)			
Degree of stenosis (% area)	68 ±15·6%		47 ±15·6%*
Prestenotic diameter	3·17 ±0·63		3·31 ±0·58†
Stenotic diameter (mm)	1·71 ±0·47		2·41 ±0·55‡

Group A = 16 patients; Group B = 8 patients; n = number of stenoses. *p < 0·025; † NS; ‡p < 0·05.

cent area, isosorbide dinitrate had virtually no effect (group A of Table 2). The degree of obstruction before and after isosorbide dinitrate averaged 70±17·3 per cent and 69±17·5 per cent, respectively. The prestenotic diameters showed variable changes after nitrate, ranging between -6 and +27 per cent of the original diameter, but the average increase in prestenotic diameter did not exceed 8 per cent (from 2·82±0·48 mm to 3·05±0·43 mm). The average stenotic diameter increased only by 10 per cent (from 1·45±0·49 mm to 1·59±0·51 mm). None of these differences was significant.

In contrast, in eight other patients with nine stenoses (group B of Table 2) isosorbide dinitrate significantly enlarged the stenotic diameter. In this group the degree of stenosis before the nitrates ranged from 35 to 89 per cent area stenoses and the mean decrease in the degree of stenoses after isosorbide dinitrate was 32±10 per cent. The stenotic diameters increased in all these stenoses and the range varied between +8 and +83 per cent (mean 44±22%). The prestenotic segments, however, showed a non-uniform response since the changes in the measured diameters varied between -11 and +50 per cent, but the average increase in prestenotic diameter was only 4 per cent (from 3·17±0·63 mm to 3·31±0·58 mm) and not significant. The significant ($p < 0.025$) decrease in the average degree of stenosis from 68±15·6 to 47 ±15·6 per cent can therefore unequivocally be attributed to a significant increase of the mean stenotic diameter that enlarged from 1·71±0·47 mm to 2·41±0·55 mm.

Discussion

Nitrates cause generalised relaxation of vascular smooth muscle. Dilatation of large coronary arteries after administration of nitrates has repeatedly been shown angiographically. In the intact coronary arterial system the resistance to flow is mainly regulated at the precapillary level and is greatly influenced if not completely determined by the metabolic demands of the myocardium. Therefore, dilatation of the "conduit" vessels should not be a major determinant of coronary blood flow. Our own results examining the effect of nitrates on normal coronary arteries are in complete accordance with those studies previously reported.[5 6]

In contrast to the uniform dilatation observed in normal coronary arteries after administration of isosorbide dinitrate, a distinctively different response to the same dose of nitrates was observed in patients with coronary artery disease. Though in the majority of coronary artery stenoses the degree of obstruction was not significantly diminished by the nitrates, *no less* than one-third of the obstructions showed evidence for a significant decrease in the degree of stenosis. In the group without response the absence of a substantial decrease in the degree of stenosis is probably the result of fibrosis and/or calcification of the diseased vessel. Numerous anatomical studies have shown that foci of calcifiation can occur in almost every arteriosclerotic lesion. Calcium deposits develop independently of the severity of coronary stenosis and have sometimes been shown to invade the whole vascular circumference.[12 13] Even in the prestenotic segment, which always appeared normal in our angiographic study, undetectable intramural calcium deposits could resist pharmacological dilatation in spite of adequate relaxation of the vascular smooth muscle.

Most importantly, this study shows that stenoses of any degree and at any site can dilate in response to nitrates. In other words, the chance for a beneficial response to nitrates is as good in a stenosis with high degree of obstruction as in a stenosis with a low degree of obstruction. In four patients with two stenoses each, isosorbide dinitrate dilated one stenosis without affecting the other, showing that there can be a different response by different stenoses even in the same patient.

Since stenoses can dilate as shown in the present study and constrict[14] after pharmacological manoeuvres, it seems reasonable to assume that tonic dynamic changes will often and perhaps continuously influence the stenotic cross-section area. Optimal evaluation of coronary artery lesions will thus need to include a more detailed assessment of the functional anatomy of coronary artery stenoses.

Non-uniform responses of different segments of the coronary tree have already been observed by several authors.[15–20] Most of them focused on the difference between large and small coronary arteries and attributed the variable response to different neural receptors,[15 16] different smooth muscle cell membrane properties,[17–19] or even to a different pharmacological behaviour of smooth muscle.[20] Sympathetic stimuli normally dilate epicardial coronary arteries but constriction usually occurs after beta-receptor blockade.[21] A comparable observation was made when serotonin, a potent dilator of coronary arteries, was shown to cause vasoconstriction when there was decreased neurogenic tone.[22] From these and similar observations it is apparent that the pharmacological response of coronary arteries can change and that it is greatly affected by variations of autonomic nervous influences. A similar mechanism involving abnormal autonomic discharge in the atherosclerotic segment could interfere with the usually expected vasodilatation produced by nitrates.

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Br Heart J 1980; **43**: 550–5

Comparison of vasodilator drug prazosin with digoxin in aortic regurgitation*

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SUMMARY Intravenous administration of the vasodilator sodium nitroprusside has beneficial haemodynamic effects in subjects with severe aortic regurgitation while acute digitalisation can produce unwanted effects associated with an increase in systemic vascular resistance. This study compares the haemodynamic effects of the vasodilator prazosin and digoxin in eight patients with isolated severe aortic regurgitation. Prazosin 5 mg orally resulted in a 12±3 (SE) per cent increase in cardiac index (thermodilution), maintained over four to six hours, while digoxin 0·75 mg intravenously did not change the cardiac index. Prazosin reduced mean arterial pressure by 9±3 mmHg and systemic vascular resistance by 18±4 per cent while digoxin resulted in a 6±2 per cent increase in the latter. Mean pulmonary capillary wedge pressure fell 3 mmHg with prazosin. In this group of patients with severe aortic regurgitation but without severe cardiac failure, the changes with either drug, studied in doses conventionally used, were small but those with prazosin were directionally more desirable than those resulting from digoxin.

This study describes and compares the haemodynamic effects of the orally active vasodilator drug prazosin and digoxin in a group of patients with severe chronic aortic regurgitation.

Corrigan,[1] writing in 1832, believed that when digitalis glycosides were administered in the treatment of heart failure resulting from aortic regurgitation, the patients were "always worse". He attributed the harmful effects he observed to bradycardia which "allowed more time for regurgitation". In 1908, Stewart[2] predicted harmful effects from digitalis in aortic regurgitation because of a rise in the systemic vascular resistance. Objective evidence of the haemodynamic effects of the digitalis glycosides in the presence of aortic regurgitation is sparse. Kloster and associates[3] found that ouabain resulted in a fall in cardiac output in patients with aortic regurgitation without cardiac failure while Hopkins and Taylor[4] found that ouabain and acetylstrophanthidin increased the regurgitant fraction in dogs with experimentally induced aortic regurgitation.

In contrast, the intravenous administration of the vasodilator sodium nitroprusside has been shown to produce distinct haemodynamic improvement in patients with severe aortic regurgitation. Nitroprusside exerts a beneficial effect by decreasing both preload and afterload, the latter resulting in an increase in forward cardiac output and frequently a reduction in the regurgitant fraction.[5 6]

Notwithstanding this, digitalis glycosides are frequently used in the treatment of patients with aortic regurgitation, sometimes even before overt signs of cardiac failure develop. Theoretically at least, an orally acting vasodilator drug could be a more rational approach to the treatment of such patients. Prazosin is a vasodilator agent which is available in oral form and which possesses properties similar to those of sodium nitroprusside, acting on both the capacitance and resistance vascular beds.[7] While prazosin has been used in the management of patients with resistant cardiac failure,[8 9] the effects of the drug on the circulation of patients with aortic regurgitation have not previously been described.

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* Supported in part by grants from the National Heart Foundation of Australia and the Royal Perth Hospital Research Foundation.

Received for publication 26 November 1979

Subjects and methods

Eight patients, seven men and one woman, consented to the study. Their mean age was 46 years. They all had chronic severe isolated aortic regurgitation documented clinically and by cardiac catheterisation and aortography. Five patients had a history of probable rheumatic fever and one patient had pathological evidence of cystic medial necrosis in the aortic valve when it was subsequently excised. The aetiology of the aortic regurgitation in the other two patients is unknown. Selective coronary angiography showed the absence of obstructive coronary artery disease in all subjects. No patient had previous cardiac surgery and though all were candidates for, and subsequently underwent, aortic valve replacement, no patient was deemed to be critically ill at the time of study. All were in sinus rhythm; other details are shown in Table 1. One patient was in New York Heart Association (NYHA) class I, four patients were in class II, and three were in class III. Three patients were not taking any medication, one was taking digoxin alone, two were taking diuretics alone, and two were taking both digoxin and diuretics.

Patients were admitted to the coronary care unit for study. When treatment included digoxin, this was stopped one week before, while all other drugs were withheld for at least 24 hours. A 20 gauge Teflon catheter was inserted into a radial artery and used to record systemic arterial pressure. Right atrial, pulmonary arterial, and pulmonary capillary wedge pressures were obtained using a 7F balloon tipped thermodilution flotation catheter (Edwards Laboratories Inc), which was inserted percutaneously. Pressures were measured using Bentley 800 transducers (Bentley-Trantec Inc), and were displayed on a multichannel recorder (Irex Medical Systems). Cardiac output was measured by thermodilution (Edwards Laboratories Inc) using iced 5 per cent dextrose, the measurement being taken as the mean of three readings having less than 10 per cent variation between them. Echocardiograms were obtained using a Smith Kline Ekoline 20A and a 2·5 MHz transducer (Smith Kline Instruments Inc). Standard techniques for recordings and measurements were used.[10] Echocardiograms of suitable quality for accurate measurement of left ventricular dimensions were obtained in six out of the eight patients. Measurements were made by an observer unaware of the relation of the timing of the recording to the administration of the drugs.

Patients were studied in the postabsorptive state. After baseline haemodynamic measurements and an echocardiogram had been obtained, the subjects were given prazosin 1 mg orally and observations were repeated an hour later. Recording cannulae were left in place, and the next morning 5 mg prazosin was given after control observations. Pressure and cardiac output measurements were repeated at 30-minute intervals for two hours and then hourly up to six hours. An echocardiogram was obtained during the period of maximal haemodynamic effect of the drug, one-and-a-half to two hours after administration. On the third day, after control observations, digoxin (Burroughs Wellcome) 0·75 mg was given intravenously over 10 minutes. Pressures and cardiac output were measured at hourly intervals for six hours and echocardiography was repeated when maximal haemodynamic effects of the drug were apparent, approximately three hours after administration.

Derived haemodynamic indices were calculated as follows: systemic vascular resistance (SVR dynes s cm^{-5}) from $((\overline{AP} - \overline{RA}) \times 80)/CO$; where $\overline{AP}$ is mean radial arterial pressure, $\overline{RA}$ is mean right atrial pressure, 80 is the conversion factor for converting units of resistance into dynes, and CO is cardiac output; pulmonary vascular resistance (PVR dynes s cm^{-5}) from $((\overline{PA} - \overline{PCW}) \times 80)/CO$;

Table 1 *Eight patients with aortic regurgitation—clinical information*

Patient	*Age (y)*	*Symptoms*	*NYHA* classification*	*Duration of aortic regurgitation (y)*	*Drugs daily*
Male	37	Dyspnoea	II	24	Digoxin 0·5 mg
Male	22	Dyspnoea, chest pain	II	Unknown	Nil
Male	53	Dyspnoea, chest pain	II	Unknown	Nil
Male	59	Dyspnoea, chest pain	III	43	Frusemide 40 mg
Male	49	Dyspnoea	III	Unknown	Frusemide 40 mg, digoxin 0·25 mg
Male	36	Nil	I	23	Nil
Female	49	Dyspnoea, chest pain	III	42	Hydrochlorothiazide 100 mg, amiloride hydrochloride 10 mg, digoxin 0·25 mg
Male	59	Dyspnoea, chest pain	II	32	Cyclopenthiazide 0·5 mg

*New York Heart Association classification.

where $\overline{PA}$ is mean pulmonary arterial pressure and $\overline{PCW}$ is mean pulmonary capillary wedge pressure; stroke work index (SWI g m per m^2) from $(\overline{AP} - \overline{PCW}) \times (CI/HR) \times 0{\cdot}0136$ when CI is cardiac index and HR is heart rate.

For statistical analysis changes induced by each drug were expressed as percentage changes and the significance of each mean percentage change was evaluated using Student's t test rather than using analysis of paired comparisons in individual patients.

Results

There were no relevant side effects from either digoxin or prazosin, and all the patients who entered the study were able to complete it. No untoward effects were apparent from stopping digoxin a week before study in those patients on the drug.

Results of prazosin and digoxin administration are summarised in Table 2. Maximum effects of prazosin 5 mg were present at one-and-a-half to two hours and of digoxin at three hours and these are the results presented in this Table. The time course of changes in cardiac index, mean pulmonary capillary wedge pressure, mean arterial pressure, systemic vascular resistance, and heart rate produced by the two drugs is illustrated in the Fig.

Prazosin 5 mg resulted in a fall in systemic vascular resistance of 18 per cent ($p < 0{\cdot}005$) and a smaller fall in systemic arterial pressure since cardiac index rose 12 per cent ($p < 0{\cdot}005$). Mean pulmonary capillary wedge pressure fell and though this fall was only 3 mmHg it was significant ($p < 0{\cdot}01$). Heart rate increased 4 beats/min while changes in pulmonary vascular resistance, central venous pressure, and stroke work were not significant. There were no significant differences between the effects of the first dose of prazosin 1 mg and the second of 5 mg.

In contrast to the results with prazosin, digoxin increased systemic vascular resistance 6 per cent ($p < 0{\cdot}05$) and there was no change in cardiac index (Table 2). Heart rate slowed 6 beats/min ($p < 0{\cdot}01$). There was a small fall in pulmonary capillary wedge pressure which was not significant.

Echocardiograms of suitable quality were obtained in six out of eight patients. All six patients had distinctly increased left ventricular end-diastolic dimensions and in three of the six the fraction of shortening was less than 25 per cent. There was no significant change in end-diastolic dimension or fractional shortening after either prazosin 5 mg or digoxin 0·75 mg.

Three of the eight patients had pulmonary capillary wedge pressures greater than 15 mmHg, two of these also having fractional shortening less than 25 per cent, but the results in these patients with evidence of depression of left ventricular function were not obviously different from those of the other patients.

Discussion

The magnitude of regurgitation through an incompetent aortic valve depends not only upon the pathology of the valve but also upon other circula-

Table 2 *Haemodynamic changes with prazosin and digoxin in patients with aortic regurgitation*

	CI (l/min per m²)	*PCW (mmHg)*	*MAP (mmHg)*	*SVR (dynes s cm⁻⁵)*	*PVR (dynes s cm⁻⁵)*	*HR (beats/min)*	*RA (mmHg)*	*SWI (g m per m²)*	*EDD (cm)*	*FS (%)*
Control	3·3	14	88	1072	85	72	8	47	7·1	21
Prazosin 1 mg	3·6	11	80	883	92	81	6	46	6·9	27
Per cent change (±SE)	+14 ±4	−21 ±5	− 9 ±4	−19 ±3	+16 ±6	+9 ±3	−18 ±10	−2 ±5	−4 ±4	+6 ±3
Significance of change	p < 0·01	p < 0·005	p < 0·05	p < 0·001	NS	p < 0·02	NS	NS	NS	NS
Control	3·3	12	84	1127	116	74	5	43	7·0	25
Prazosin 5 mg	3·7	9	76	914	93	78	5	43	7·1	28
Per cent change (±SE)	+12 ±3	−26 ±7	− 9 ±3	−18 ±4	−13 ±13	+6 ±2	0 ±1	−1 ±3	+2 ±2	+3 ±2
Significance of change	p < 0·005	p < 0·01	p < 0·05	p < 0·005	NS	p < 0·02	NS	NS	NS	NS
Control	3·4	14	88	1101	75	75	7	46	7·2	27
Digoxin 0·75 mg	3·3	12	89	1171	91	69	6	50	7·2	31
Per cent change (±SE)	−3 ±2	−10 ±5	+2 ±2	+6 ±2	+29 ±18	−8 ±2	−3 ±8	+12 ±6	0 ±2	+4 ±2
Significance of change	NS	NS	NS	p < 0·05	NS	p < 0·01	NS	NS	NS	NS
Significance*	p < 0·001	NS	p < 0·02	p < 0·001	NS	p < 0·001	NS	NS	NS	NS

CI, cardiac index; PCW, pulmonary capillary wedge pressure; MAP, mean radial arterial pressure; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; HR, heart rate; RA, right atrial pressure; SWI, stroke work index; EDD, end-diastolic dimension; FS, fraction of shortening; SE, standard error; NS, not significant.

* Significance between group mean changes induced by prazosin 5 mg and digoxin 0·75 mg.

tory variables, including the diastolic pressure gradient across the valve and the duration of diastole.[11–13] The decrease in systemic vascular resistance produced by drugs such as isoprenaline and glucagon has been shown to decrease regurgitant fraction under experimental conditions allowing accurate measurement of ascending aortic blood flow.[4 14] Reduced impedance enhances forward flow, and regurgitant flow diminishes concurrently if the diastolic aorto-ventricular pressure gradient is reduced. In human subjects with aortic regurgitation, intravenous sodium nitroprusside, which produces dilatation of both the systemic resistance and capacitance beds, has been shown to reduce left ventricular end-diastolic pressure and volume, to increase forward cardiac index and ejection fraction, and frequently to reduce aortic regurgitant fraction. Vasodilator therapy with nitroprusside has become established as one of the most effective forms of temporary medical treatment before valve replacement in the critically ill patient with aortic regurgitation.[5 6] Since prazosin, a post-synaptic alpha-adrenergic blocker, also acts on resistance and capacitance beds, but can be administered orally, and is effective in the management of patients with resistant cardiac failure,[8 9 15] it was considered important to document some of the haemodynamic effects of prazosin in patients with severe aortic regurgitation. Prazosin reduced systemic vascular resistance 18 per cent, increased cardiac index 12 per cent, and led to a small fall in pulmonary capillary wedge pressure. These changes were not associated with consistent changes in left ventricular dimensions measured echocardiographically.

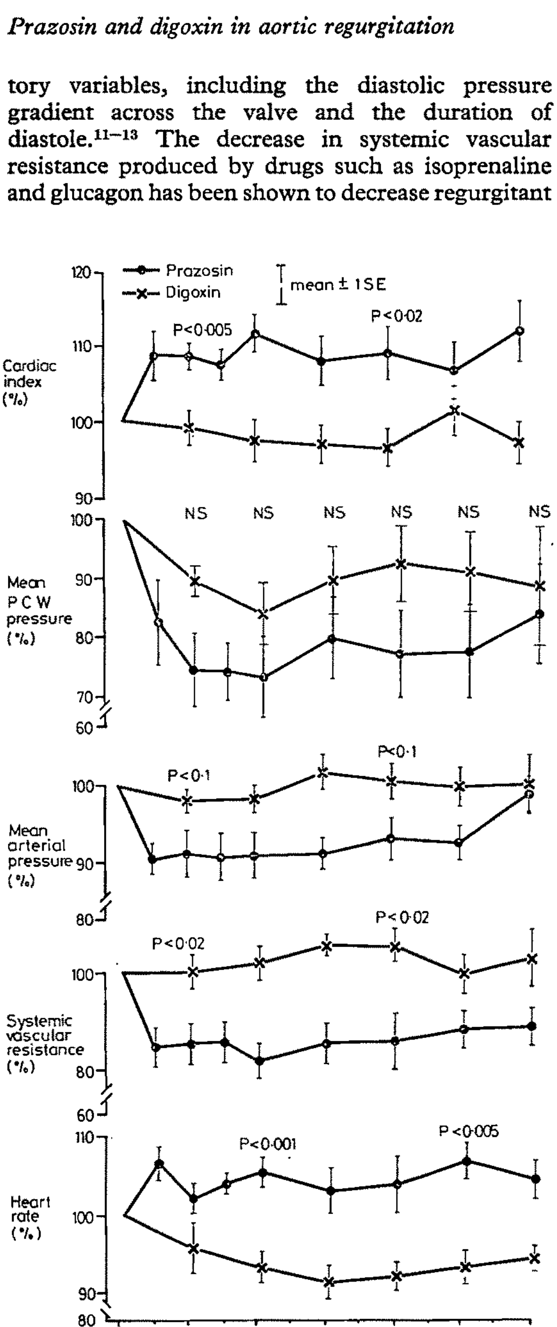

Fig. *Haemodynamic changes after prazosin and digoxin. The time course of haemodynamic changes after a single tablet of prazosin 5 mg and a single intravenous injection of digoxin 0·75 mg in the eight patients with chronic aortic regurgitation. Average values ± SEM are shown; p values shown on the figure relate to the significance of difference between group mean measurements after prazosin and digoxin.*

The patients studied had severe but chronic stable aortic regurgitation and the results cannot be extrapolated directly to other groups. It is now widely appreciated that dilatation and hypertrophy allow compensation in terms of resting left ventricular end-diastolic pressure and cardiac output until late in the natural history of chronic aortic regurgitation. Though our patients as a group were quite symptomatic, only three had abnormal mean pulmonary capillary wedge pressures which, in this situation, probably indicate some depression of myocardial function.[16] The haemodynamic situation in acute torrential regurgitation is often quite different, with pronounced rises in left ventricular end-diastolic pressure, premature mitral valve closure, and circulatory failure.

We studied the effects of digoxin because digitalis is frequently given to patients with severe aortic regurgitation despite the absence of obvious cardiac failure or atrial fibrillation. The little objective evidence available has actually suggested that there might be a deleterious effect in patients such as those studied. In the dog with aortic regurgitation, acute digitalisation increases systemic vascular resistance and regurgitant flow. Despite the positive inotropic effect of the glycosides, left ventricular end-diastolic pressure increases.[4] In patients with chronic aortic regurgitation and without cardiac failure Kloster and associates[3] found that intravenous ouabain resulted in an increase in systemic vascular resistance and a decrease in resting cardiac output, with only a trivial fall in left heart filling pressures. In this present study digoxin was given intravenously to ensure that a known quantity of the drug was active at the time of haemodynamic monitoring. Cardiac glycosides have been shown to have different effects on systemic vascular resistance and arterial pressure depending on the rate of intravenous infusion.[17] Early after the intravenous administration of some cardiac glycosides the increase in systemic vascular resistance may precede direct cardiac effects.[17] This, however, is not relevant to the observations three hours after intravenous digoxin when the cardiac inotropic effect would be expected to be maximal.[18] There are no important differences between slow intravenous and acute oral administration but it is possible that there are differences in effects between acute and chronic treatment. In this study we were particularly interested in the effects of digoxin at times greater than one hour after drug administration when haemodynamic indices are not affected by the rate of intravenous administration and changes parallel the effects of orally administered glycosides. We did not find any evidence of a harmful effect but the beneficial effect was minimal. Nevertheless, in patients with obvious cardiac failure digitalis may reduce rather than increase systemic vascular resistance,[19] and we emphasise again that the effects of digitalis in patients with aortic regurgitation and severe cardiac failure are unknown.

This study was confined to relatively simple measurements under resting conditions without any attempt to measure regurgitant flow. Other constraints were imposed by ethical considerations; for example, digoxin was always administered after prazosin. This was accepted because of the relatively short plasma half life of prazosin, two-and-a-half to four hours,[20] and because, in the 24-hour interval allowed, recordings returned to control levels. Reversal or randomisation of the order would have required an interval of at least several days and this was considered unjustified since the procedure already required two days of invasive monitoring.

While interpretation must, then, be cautious, the results give little support for the use of digitalis glycosides in patients with severe aortic regurgitation in the absence of a more specific indication such as atrial fibrillation with rapid ventricular response. It remains conjectural whether long-term vasodilator therapy will be beneficial in the patient group we studied, either in reducing symptoms or in slowing deterioration of ventricular function but, in principle, vasodilator therapy seems to be more soundly based than prophylactic digitalisation.

The authors are grateful to Mr L Mina for assistance with the statistical analysis of the results, and to AHS Australia Pty Ltd and the University of Western Australia for financial assistance.

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Br Heart J 1980; **43:** 556-60.

Acute haemodynamic effects of oral prazosin in severe mitral regurgitation*†

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SUMMARY Acute haemodynamic effects of single dose oral prazosin were studied in eight patients with mitral regurgitation. Heart rate, mean systemic arterial pressure, pulmonary arterial pressure, left ventricular filling pressure, and forward cardiac output were measured in all patients. At peak effect, prazosin reduced mean systemic arterial pressure (95±4 to 86±4 mmHg), pulmonary arterial pressure (45±6 to 23±4 mmHg), and left ventricular filling pressure (30±4 to 21±3 mmHg). Pulmonary and systemic vascular resistance also fell (316±49 to 208±43 dynes s cm^{-5} and 2132±148 to 1491±94 dynes s cm^{-5}, respectively). Forward cardiac index increased from 1·89±0·12 to 2·43±0·13 l/min per m^2 and stroke volume from 43±5 to 57±6 ml/beat after prazosin. The onset of these changes occurred between 15 and 30 minutes, peaked between 45 and 60 minutes, and persisted for six hours. These data indicate that in patients with mitral regurgitation oral prazosin promptly improves cardiac performance (judged by increased forward cardiac output and reduced left ventricular filling pressure) as systemic and pulmonary vascular resistances are reduced.

Vasodilator treatment often improves the haemodynamic state of patients with cardiomyopathy.[1-5] Reduction in systemic vascular resistance results in augmented cardiac output, while a reduction in venous return effects a decline in left ventricular filling pressure. Administration of intravenous nitroprusside, an equipotent dilator of arterial resistance and venous capacitance vessels, increases forward cardiac output in patients with mitral[6] or aortic regurgitation[7] in association with a decrease in peripheral vascular resistance. Administration of oral hydralazine improves forward flow in mitral regurgitation and decreases the regurgitation fraction.[8] Oral prazosin has been shown to exert dilatating effects on arterial and venous beds qualitatively similar to the effects of intravenous nitroprusside.[9] Prazosin increases cardiac output and decreases left ventricular filling pressure in patients with heart failure.[9-11] The haemodynamic effects of oral prazosin in patients with mitral regurgitation have not been reported.

The purpose of this study was to evaluate the acute effects of oral prazosin on forward cardiac output and left ventricular filling pressure in patients with mitral regurgitation.

Methods

PATIENTS

The study group comprised eight men (aged 24 to 65 years) with severe mitral regurgitation. At the time of study, all subjects were in the New York Heart Association[12] functional class III or IV. Three of these patients also had coronary heart disease documented by history, electrocardiograms, and coronary angiography. None had angina at the time of study. No localised abnormalities were observed on the left ventriculogram. Angiographically, the severity of mitral regurgitation varied from 3+ to 4+. Six of these patients were receiving digitalis and diuretics: digitalis was continued but diuretics were withdrawn two days before the study. None of the patients was taking nitrates or other vasodilators.

HAEMODYNAMIC STUDIES

The procedure was carefully explained to all

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* This study was supported in part by a grant from the Veterans Administration.

† Presented in part at the annual meeting of the Southern Society for Clinical Investigation, New Orleans, Louisiana, January 1979.

Received for publication 8 August 1979

patients and informed consent was given by them. They were kept in bed for at least eight hours before the study to achieve a steady state, and were moved to a special study room of the cardiac care unit so that haemodynamic variables could be monitored and recorded for long periods.

A triple lumen flow-directed catheter was inserted into the pulmonary artery. A Teflon catheter was placed percutaneously into the radial artery to measure systemic blood pressure. Systemic and pulmonary arterial pressures and pulmonary capillary wedge pressures were recorded on an Electronics for Medicine VR6 recorder with P 231a Statham strain gauge transducers. Mean pressures were obtained by electronic filtration. All pressure measurements were referenced to the mid-chest. Heart rate was averaged from recordings of a standard electrocardiographic lead. Cardiac output was measured in triplicate with the thermodilution technique[13] using a thermodilution computer (Edwards Laboratory, Santa Ana, California), and the data are reported as the average of these three determinations. All the haemodynamic measurements were made in these patients for eight hours.

CALCULATIONS

The following calculations were made:

CI = CO/BSA l/min per m^2
SV = CO/HR ml/beat
LVSWI = SVI × ($\overline{Ao}$ − LVFP) × 0·0136 g m per m^2
SVR = $\overline{Ao}$ × 80/CO dynes s cm^{-5}
PVR = ($\overline{PA}$ − LVFP) × 80/CO dynes s cm^{-5}

Where CI = cardiac index, CO = cardiac output, BSA = body surface area, SV = stroke volume, HR = heart rate, SVI = stroke volume index, LVSWI = left ventricular stroke work index, $\overline{Ao}$ = mean arterial pressure, LVFP = left ventricular filling pressure, SVR = systemic vascular resistance, PVR = pulmonary vascular resistance, $\overline{PA}$ = mean pulmonary artery pressure.

STUDY PROCEDURE

Haemodynamic measurements were made repeatedly until a stable state was achieved. The patients were considered to be stable when haemodynamic variables were within 10 per cent on multiple measurements. Each patient was then given a single 4 mg dose of oral prazosin. Haemodynamic data were recorded every 15 minutes for the first hour and then every hour for the additional seven hours.

STATISTICS

Mean and standard error of the mean were calculated. The paired Student t test was used to determine the statistical significance of comparisons between the control and peak effect periods. A probability (p) value of less than 0·05 was considered significant.

Results

Haemodynamic effects were observed between 15 and 30 minutes after oral prazosin, peaked between 45 and 60 minutes, and persisted for approximately six hours (Table). Changes in haemodynamic variables at peak effect are shown in Fig. 1 to 5.

Heart rate decreased slightly in all but two patients after oral prazosin (92 ± 7 to 88 ± 5 beats/min, p = NS). A 9 per cent decline in mean arterial pressure from 95 ± 4 to 86 ± 4 mmHg ($p < 0{\cdot}005$)

Table *Haemodyamic responses in control state, and after prazosin administration*

		Pressures (mmHg)							
	Heart rate (beats/min)	*Mean systemic arterial*	*Mean pulmonary arterial*	*Left ventricular filling*	*Cardiac index (l/min per m²)*	*Stroke volume (ml/min)*	*LVSWI (g m per m²)*	*SVR*	*PVR*
								(dynes s cm⁻⁵)	
Control									
Mean	92	95	45	30	1·89	43	19·6	2132	316
± SEM	7	4	6	4	0·12	5	2·7	148	49
Peak effort (1 to 6 h) of prazosin									
Mean	88	86	33	21	2·43	57	26·7	1491	208
± SEM	5	4	4	3	0·13	6	3·8	94	43
Eight hours after prazosin									
Mean	90	92	40	26	2·12	51	22·1	1653	269
± SEM	6	5	5	4	0·13	7	3·9	112	54

LVSWI, left ventricular stroke work index; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

was observed (Fig. 1). Cardiac index increased from 1·89 ±0·12 to 2·43 ±0·13 l/min per m^2 ($p < 0{\cdot}001$). Stroke volume increased from 43 ±5 to 57 ±6 ml/beat ($p < 0{\cdot}001$). Increases in cardiac index and stroke volume were observed in each patient (Fig. 2). Left ventricular stroke work index also increased in each patient (mean 19·6 ±2·9 to 26·7 ±3·8 g m per m^2 ($p < 0{\cdot}01$).

A significant decline in mean pulmonary artery pressure from 45 ±6 to 33 ±4 mmHg ($p < 0{\cdot}02$) occurred. Left ventricular filling pressure decreased from 30 ±4 to 21 ±3 mmHg ($p < 0{\cdot}01$). These changes in mean pulmonary artery and left ventricular filling pressures were noticed in each patient studied (Fig. 3). The "v" wave in the pulmonary artery wedge pressure tracing gradually decreased in each patient from a mean of 40 ±6 to 20 ±4 mmHg ($p < 0{\cdot}001$). The gradual decline in "v" wave after prazosin administration in a patient is shown in Fig. 4.

Systemic and pulmonary vascular resistance decreased in each patient studied with a single dose of prazosin. At peak effect, systemic vascular resistance was reduced from 2132 ±148 to 1491 ±94 dynes s cm^{-5} ($p < 0{\cdot}001$). Similarly, pulmonary vascular resistance declined from 316 ±49 to 208 ± 43 dynes s cm^{-5} ($p < 0{\cdot}005$) (Fig. 5).

CLINICAL EVALUATION

Six of the eight patients reported noticeable improvement in symptoms of low cardiac output such as fatigue and weakness. Subjectively, dyspnoea decreased considerably in five and to a lesser degree in the remaining three patients. Examination disclosed that the extremities were warmer than in the period before prazosin. The intensity of the mitral regurgitation murmur decreased in seven patients.

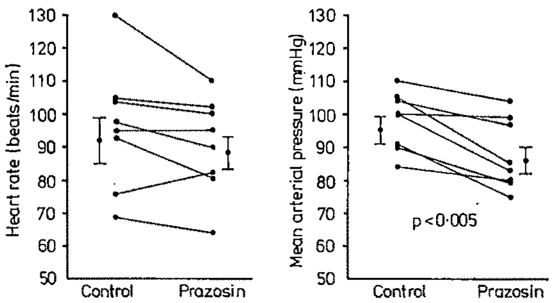

Fig. 1 *Peak effects of oral prazosin in patients with severe mitral regurgitation. Heart rate* (left) *was unchanged, while mean arterial pressure* (right) *declined significantly.*

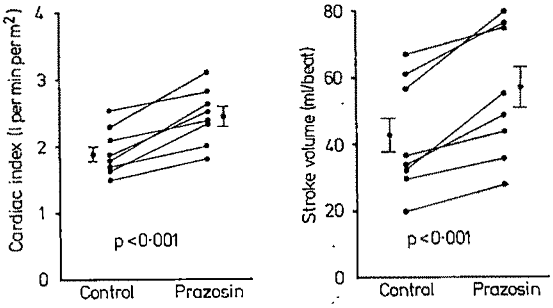

Fig. 2 *At peak effect, oral prazosin increased cardiac index* (left) *and stroke volume* (right) *in each patient.*

SIDE EFFECTS

No untoward effects were observed with administration of prazosin. None of the patients manifested hypotension, tachycardia, or evidence of myocardial ischaemia. No cardiac arrhythmias were observed. Overall, all patients tolerated single dose prazosin without any side effects.

Discussion

Systemic vascular resistance is one of the important determinants of left ventricular function.[14] It has been shown that an increase in systemic vascular resistance may be detrimental, whereas a decrease may be beneficial in heart failure.[15, 16] Most patients with heart failure also have an increase in blood volume (preload) which in the early stages of heart failure is a compensatory phenomenon to maintain cardiac output.[4] Nevertheless, persistently raised preload may be detrimental to left ventricular performance because of increased heart size. In several studies[9, 16–18] salutary effects of nitroprusside infusion in heart failure patients have been shown. These effects are thought to be related to a simultaneous decrease in both afterload and preload by nitroprusside. Load reduction therapy with nitroprusside also improves forward cardiac output and decreases regurgitant fraction in valvular regurgitant lesions.[6, 7, 19] However, nitroprusside therapy is limited to patients in hospital because it has to be administered intravenously. Moreover, the haemodynamic effects of nitroprusside last only for the duration of the infusion.

The results of our study show that oral prazosin resulted in an improved haemodynamic response in patients with severe chronic mitral regurgitation and heart failure. Forward cardiac output and stroke volume increased. Simultaneously, a significant decline in pulmonary artery and left ventricular filling pressures occurred. These effects occurred in association with a distinct decrease in resistance in

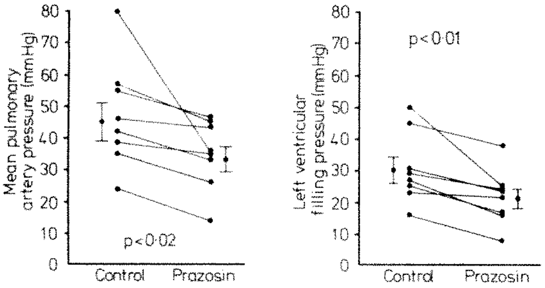

Fig. 3 *Oral prazosin administration resulted in a decline in mean pulmonary artery* (left) *and left ventricular filling pressures* (right) *in each patient.*

both systemic and pulmonary vascular beds. In each patient with mitral regurgitation, the amplitude of the regurgitant "v" wave observed in the pulmonary wedge pressure tracing declined. Since heart rate and arterial pressure fell slightly, it is unlikely that the myocardial oxygen demands increased, while the left ventricular performance improved.

In this study, the haemodynamic effects of oral prazosin were first observed between 15 and 30 minutes after administration, peaked between 45 and 60 minutes, and persisted for six hours. These observations on the onset and duration of action are similar to those previously reported by us,[9, 20] and others.[10, 11]

The precise mechanism responsible for a vasodilator-associated increase in forward cardiac output in patients with valvular regurgitation lesions and heart failure is not known. It has been suggested that a decrease in systemic vascular resistance by vasodilators results in improved forward cardiac output and reduced regurgitation fraction.[6, 7, 19] Studies in our laboratory have shown that in patients with heart failure, the compliance of the aorta is decreased and the vascular load much increased.[21] Preliminary studies suggest that nitroprusside improves cardiac output in patients with heart failure while both peripheral resistance and characteristic aortic impedance decline. The latter finding also implies an alteration of aortic distensibility.[16] The present data in a small number of subjects show that indices of cardiac performance are improved by oral prazosin in patients with severe mitral regurgitation and heart failure. Though we did not directly measure the regurgitation fraction, the increases in stroke volume and stroke work index together with the reduced pulmonary capillary "v" wave suggest enhanced forward flow in association with a decrease in vascular load in these patients.

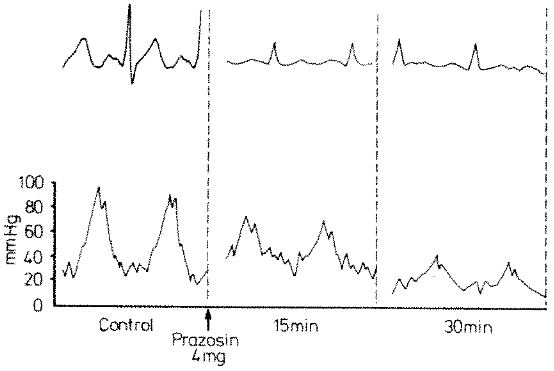

Fig. 4 *Effects of prazosin administration on "v" wave in the pulmonary artery wedge pressure in a patient with severe mitral regurgitation. A decrease in "v" wave amplitude is seen at 15 minutes with further decline at 30 minutes.*

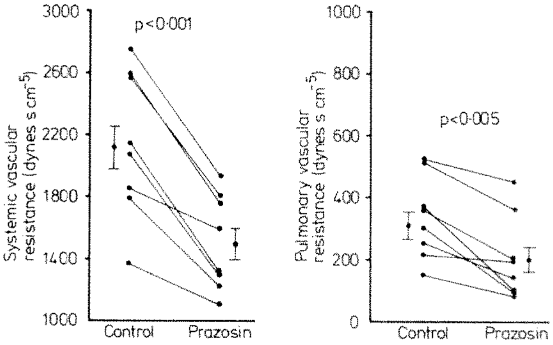

Fig. 5 *At peak effect of prazosin, systemic* (left) *and pulmonary* (right) *vascular resistances were lower compared with the control state in each patient.*

The reduction in preload resulting from prazosin may be of considerable importance in patients with mitral regurgitation. It has been suggested that left ventricular volume is an important determinant of the severity of mitral regurgitation.[22] A decrease in preload and subsequently in left ventricular volume may result in reduced valvular regurgitation, and may reduce myocardial ischaemia when present. In a study using a relatively selective afterload reducing agent, hydralazine, in patients with severe mitral regurgitation,[8] an improvement was reported in forward cardiac output related to the afterload-reducing actions of hydralazine. The investigators, however, expressed concern about the absence of a decline in left ventricular volume with this agent. Though left ventricular volume measurements were not made in our patients during treatment with prazosin, a pronounced decline in the left ventricular filling pressure at the peak effect of prazosin suggests a decreased venous return to the left heart, hence a decrease in left ventricular volume. Dilatation of the venous capacitance bed by prazosin[11] may complement its afterload-reducing effects in patients with severe mitral regurgitation.

A pronounced decrease in symptoms of fatigue and dyspnoea as reported by our patients is probably a manifestation of enhanced cardiac output and reduced pulmonary pressure. In addition, a decrease in intensity of the mitral regurgitation murmur suggests a decrease in regurgitant volume.

In summary, our study shows that in patients with severe mitral regurgitation and heart failure, components of left ventricular afterload (systemic vascular resistance) and preload (left ventricular filling pressure) decline after prazosin. These haemodynamic effects result in improved cardiac performance, that is increased forward cardiac output and reduced left ventricular filling pressure. Prazosin may be a potentially useful agent in patients with severe mitral regurgitation. Furthermore, absence of cardiostimulatory properties may make prazosin useful in patients with mitral regurgitation associated with ischaemic heart disease.

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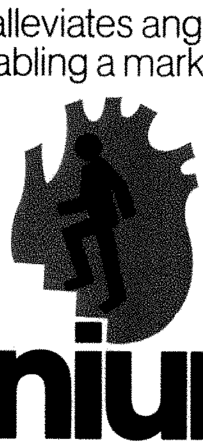

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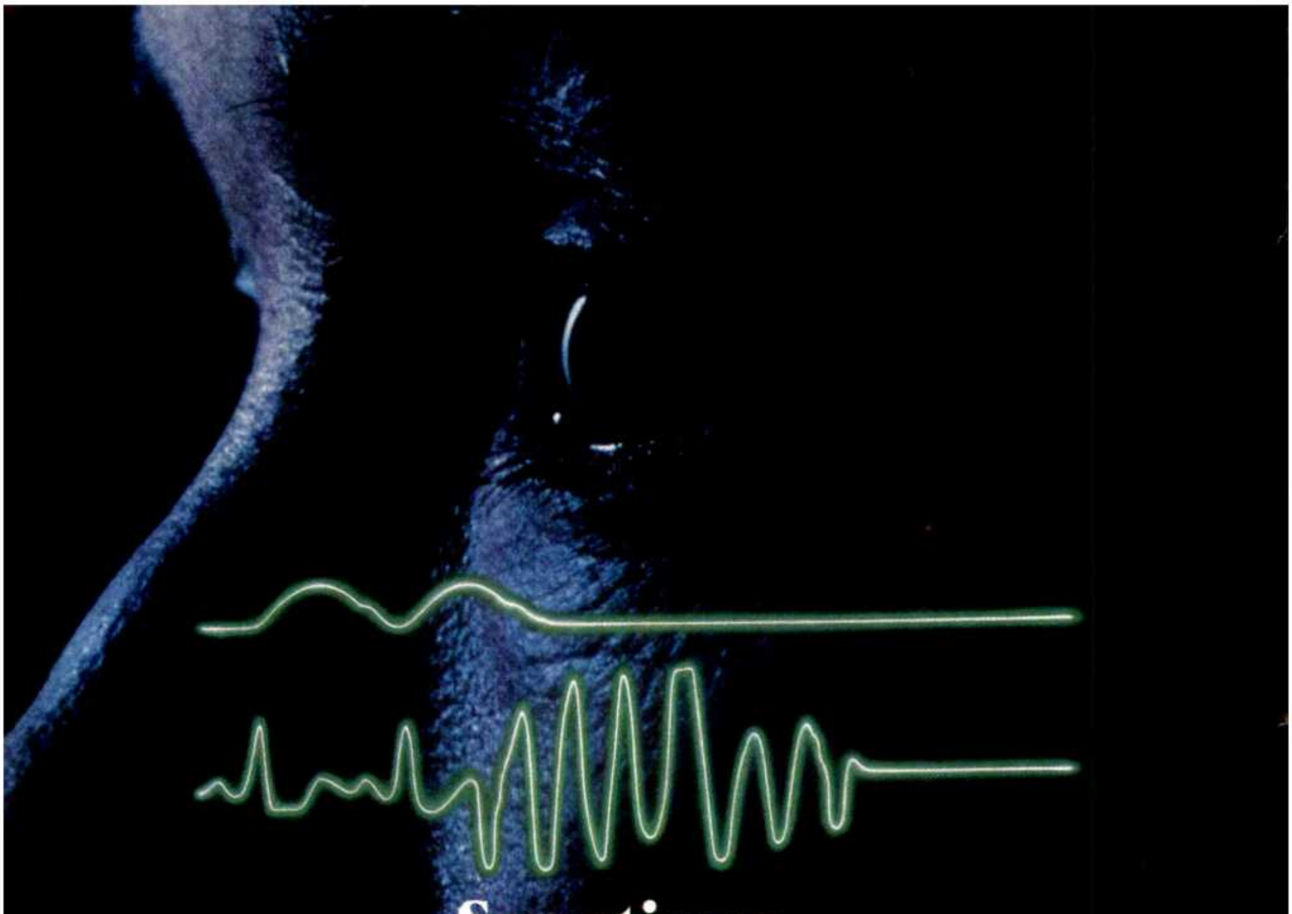

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Br Heart J 1980; **43**: 561–73

Congenital valvar aortic stenosis
Natural history and assessment for operation

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SUMMARY Two hundred and eighteen patients with congenital valvar aortic stenosis aged between 1 and 25 years at presentation were followed for one to 26 years (average 8·7 years). Assessment of severity of aortic stenosis was essentially based on clinical findings including symptoms, the character of the pulse, and the behaviour of the second heart sound, management being further influenced by the degree of left ventricular hypertrophy shown in the electrocardiogram. There was reasonable correlation between clinical and haemodynamic assessment and all patients with a gradient between left ventricle and aorta (LV–Ao) greater than 50 mmHg (6·7 kPa) were judged to have moderate or severe aortic stenosis on physical signs. Fifty-five per cent of those judged mild on presentation still had a mild lesion 18 years later; 42 per cent of those judged moderate on presentation still had a moderate lesion 15 years later. Forty-four patients had an operation and of the 30 patients who underwent aortic valvotomy, only 40 per cent still had a satisfactory result 13 years later. There were three preoperative and seven postoperative deaths but in only two patients was death directly related to severe aortic stenosis and both of these patients had been lost to follow-up.

It is concluded that indications for operation are aortic stenosis which is moderate or severe on physical findings, together with restrictive symptoms or ST and T wave changes on the electrocardiogram. Using these criteria, the risk of sudden death is minimal and irreversible myocardial damage unlikely. We do not recommend either routine cardiac catheterisation or routine operation at any arbitrary LV–Ao gradient.

The assessment and management of congenital aortic stenosis (AS) are still controversial. Traditionally, clinical signs, including the character of the pulse, behaviour of the second heart sound, and degree of left ventricular hypertrophy have been the main criteria of severity. Several authors[1–3] have suggested that analysis of the carotid upstroke is a helpful method of assessing severity, Gray[4] and Braunwald *et al.*[5] reported a reasonable correlation between severity and the behaviour of the second heart sound, and Marquis and Logan[6] found that electrocardiographic evidence of left ventricular hypertrophy was the most reliable single sign of severe AS. On the other hand, there have been many reports suggesting that physical findings[7–12] and the electrocardiogram[5 7 13 14] are unreliable. In most studies each factor has been analysed separately, and even when summation of factors has been attempted certain items have been omitted. For example, Eddleman *et al.*[15] excluded evaluation of the second heart sound and Ellison *et al.*[16] omitted analysis of the pulse contour.

The reported incidence of sudden death in children with congenital AS varies between 1 and 19 per cent.[6 8 17–21] Doubts about the reliability of physical signs, demonstration of increasing severity of obstruction in many patients, and concern about sudden death have led a number of authors to recommend repeated left heart catheterisation to determine whether mild lesions are becoming more severe.[9–11] Morrow *et al.*[22] stated that "the correlation presented between symptoms, physical signs and the severity of the obstruction demonstrates that the interpretations of clinical findings are not sufficiently reliable to permit them to be utilised in the important decision as to operation".

In published reports there is wide variation in the recommended indications for aortic valvotomy, with a tendency in recent years to recommend

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Received for publication 1 August 1979

earlier operation. Despite the fact that valvotomy is only a palliative procedure, this operation has been recommended for patients who are asymptomatic but have peak systolic pressure gradients between left ventricle and aorta (LV-Ao) of 50 mmHg (6·7 kPa) or more.[22–26]

We have not accepted the view that clinical assessment of the severity of the lesion is unreliable or that a peak systolic LV-Ao pressure difference of 50 mmHg (6·7 kPa) in an asymptomatic patient is an indication for operation. Admitting the variation in clinical presentation, we believe that sudden death is exceedingly rare in the absence of specific clinical findings, and contend that symptomatic and clinical assessment can provide the criteria for operation in most patients. In view of this disagreement with many previous publications we have reviewed our experience with this condition.

Patients

Patients with valvar AS referred to Green Lane Hospital in the years 1948 to 1976 inclusive have been reviewed. Because the management of AS in the young infant poses special problems, we have restricted this study to those presenting beyond 1 year of age, and we have also arbitrarily excluded those presenting beyond 25 years. A confident clinical diagnosis of congenital valvar AS was made in each patient and serial follow-up examinations were carried out. The minimal criteria for inclusion of patients with mild AS were the presence of a basal ejection murmur radiating to the carotid vessels almost always accompanied by a systolic ejection click, and prominence of the ascending aorta in the chest radiograph. Two hundred and sixty-four patients had mild congenital AS at the time of referral, but 111 of these were excluded from the study group because they had been seen on only one occasion. The study group comprises 218 patients; on referral 153 were considered to have a mild lesion, 54 a moderate lesion, and 11 a severe lesion. There were 160 male and 58 female patients. Four patients had associated coarctation of the aorta, two had coarctation of the aorta and a persistent ductus arteriosus, and one had coarctation of the aorta with pulmonary arterial branch stenoses. Two patients had Turner's syndrome. Thirteen per cent of the 218 patients had trivial or mild aortic regurgitation (AR) on presentation but patients with significant AR (i.e. a leak of sufficient magnitude to have a definite effect on the pulse) were excluded from the study. During the period under review approximately 2000 further patients were seen because of an ejection murmur, and a congenital anomaly of the aortic valve is probably the commonest lesion in this group, but only those with unequivocal signs of aortic stenosis have been included in the study.

In the follow-up study, patients last recorded as having moderate or severe stenosis have been reviewed within the past two years. Details of patients last recorded as having mild stenosis have been obtained from the last clinic review, usually within the past five years. Duration of follow-up ranged from one to 26 years (average 8·7 years).

Symptoms and physical, electrocardiographic, and radiological findings were recorded at referral and at last review for all patients, and immediately before operation in patients undergoing surgery. These details were also recorded at the time of cardiac catheterisation when this took place between referral and operation or last review. The criteria used for assessing the severity of AS on the basis of physical signs were as follows:

Mild aortic stenosis: Pulse volume and contour were normal on palpation and the second heart sound was normal.

Moderate aortic stenosis: There was a minor abnormality in one or more of the above signs. Pulse volume appeared abnormal more often than contour. Narrow inspiratory splitting of the second heart sound was allowed, but not a single second sound or reversed splitting.

Severe aortic stenosis: Any one of these three clinical features (pulse volume, pulse contour, or splitting of the second heart sound) was conspicuously abnormal.

Table 1 shows the arbitrary grading of the electrocardiogram used for the assessment of left ventricular hypertrophy. Though the voltage criteria for mild left ventricular hypertrophy are weak, the voltage criteria for moderate left ventricular hypertrophy are strict to avoid false positives.

The LV-Ao systolic pressure difference was measured at cardiac catheterisation in 65 patients.

Table 1 *Electrocardiographic criteria of left ventricular hypertrophy*

		Voltages	*T wave in left chest leads*
		S V1 + R V5 or S V2 + R V6	
Mild		35 to 60 mm	Normal
Moderate	*either*	> 60 mm	Normal
	or	35 to 60 mm	Reduced amplitude/flat/biphasic
Severe			Inverted

Seven patients had two preoperative studies and seven patients had both a pre- and a postoperative study, making a total of 79 catheterisations. Cardiac output was measured by Fick or dye dilution method on 63 occasions and aortic valve area index was calculated on 32 occasions.

Six patients developed significant AR during follow-up. In four this was a result of bacterial endocarditis and in two it was apparently spontaneous.

Forty-four patients have had operations at our hospital. Four had transventricular valvotomy (before 1959), 30 had transaortic valvotomy, one had an exploration of the aortic valve without aortic valvotomy, and nine had homograft aortic valve replacement. Three additional patients were operated on elsewhere and have not been included in the detailed surgical analysis but have been included in the actuarial curves for the progression of the severity of aortic lesions.

Differences between groups were assessed by Student's unpaired t test.

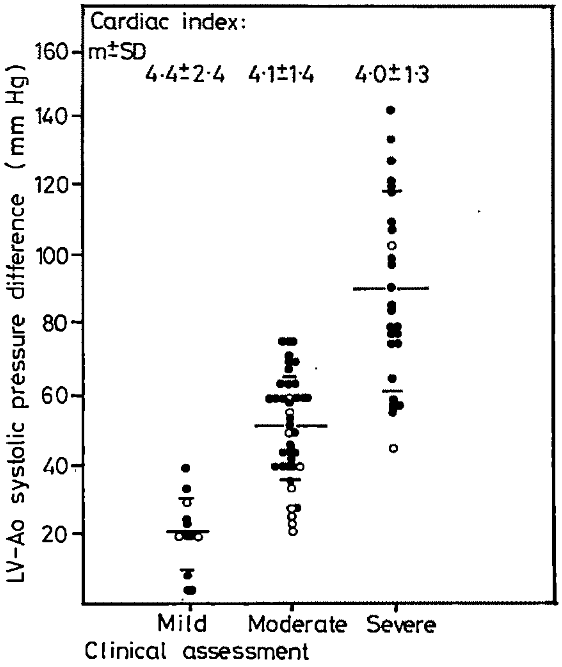

Fig. 1 *Relation between clinical assessment and peak LV–Ao systolic pressure difference. Open circles, patients with some aortic regurgitation; bars show mean values ±1 standard deviation.*
Significance of differences between groups: mild vs moderate, p < 0·001; moderate vs severe, p < 0·001; mild vs severe, p < 0·001 (1 mmHg ≈ 0·133 kPa).

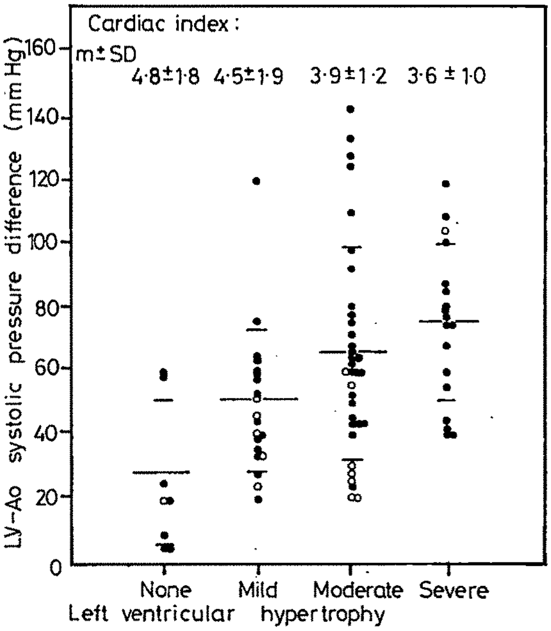

Fig. 2 *Relation between electrocardiographic assessment of left ventricular hypertrophy (LVH) and peak LV–Ao pressure difference. Significance of differences between groups: normal vs severe LVH, p < 0·001; normal vs moderate LVH, p < 0·005; normal vs mild LVH, p < 0·05; mild LVH vs severe LVH, p < 0·005; mild LVH vs moderate LVH, p < 0·05; moderate LVH vs severe LVH, NS. Seven patients had moderate LVH on voltage criteria alone.*

Results

COMPARISONS BETWEEN CLINICAL ASSESSMENT AND HAEMODYNAMIC DATA

Clinical assessment was based primarily on subjective assessment of the second heart sound and of the pulse volume and contour. In patients whose pulses were judged to be of normal volume, the measurements of pulse pressure by sphygmomanometry were 40 ± 13 mmHg (5·3 ± 1·7 kPa, mean ±1 SD), in those with a mildly abnormal pulse 32 ± 12 mmHg (4·3 ± 1·6 kPa), and in those with a conspicuously abnormal pulse 25 ± 7 mmHg (3·3 ± 0·9 kPa). Though there was a considerable overlap, the differences between each group were highly significant ($p < 0·001$) and the maximum pulse pressure in the severe group was 40 mmHg.

Thirty-one of the 218 patients presented with or developed symptoms. These were exertional dyspnoea in 19, dyspnoea and angina in six, dyspnoea and syncope in four, angina with syncope in one, and syncope alone in one. Twenty-six of these patients were assessed on physical signs as severe and five, all with dyspnoea alone, as moderate. The electrocardiogram showed severe left ventricular hypertrophy in 19, moderate in eight, and mild in three, while in one there was complete heart block. Twenty-nine of these 31 patients have had, or await, operation.

Fig. 1 shows the relation between the assessment of physical signs and the LV-Ao pressure difference in the 79 studies. All patients with a pressure difference greater than 40 mmHg (5·3 kPa) were judged moderate or severe on physical signs. Of the 23 patients with gradients greater than 75 mmHg (10·0 kPa), 87 per cent were judged as severe and the remainder moderate. Of the 39 patients with gradients between 35 and 75 mmHg (4·7 and 10·0 kPa), 82 per cent were assessed as moderate and all but one of the remainder were assessed as severe. Of the 17 patients with gradients of less than 35 mmHg (4·7 kPa), 65 per cent were assessed as mild; five of the remaining six patients had mild associated aortic regurgitation, and these and one other were assessed as moderate.

Fig. 2 shows the relation between the electrocardiographic findings and the LV–Ao pressure difference. The distinction between groups is less clear than that shown with physical signs. Examination of the interrelations between physical signs, electrocardiograms, and LV–Ao pressure differences (Fig. 3) shows that consideration of the electrocardiogram did not increase the accuracy of the clinical assessment. In the group judged moderate on physical signs, the range of LV–Ao pressure differences was similar whether the electrocardiogram showed moderate or severe left ventricular hypertrophy, the mean LV–Ao pressure difference in each case being just over 50 mmHg (6·7 kPa). In the group judged severe on physical signs, the range of LV–Ao pressure differences was again similar whether the electrocardiogram showed moderate or severe left ventricular hypertrophy; the mean was about 85 mmHg (11·3 kPa) in those with severe left ventricular hypertrophy and was actually higher in those with moderate left ventricular hypertrophy though the difference was not statistically significant.

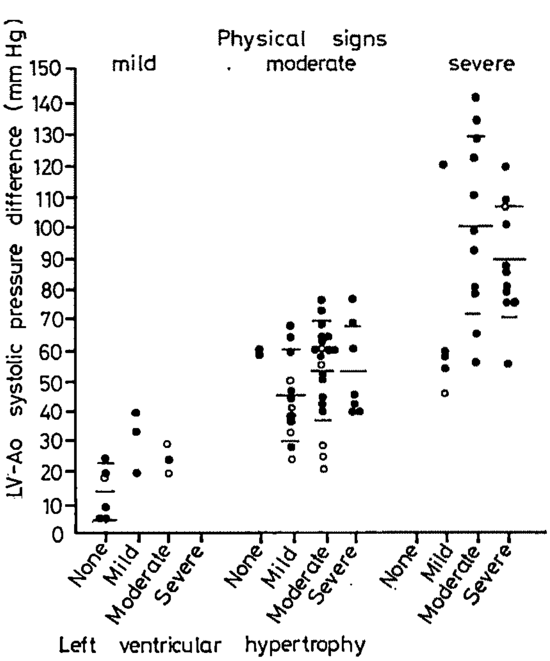

Fig. 3 *Relation between physical signs, electrocardiographic assessment, and LV–Ao pressure difference. Conventions as in Fig. 1. Patients assessed as moderate on physical signs show similar pressure gradients whether the electrocardiogram shows moderate or severe LVH: the same is true of those judged severe on physical signs, but gradients are higher than those in the moderate group.*

The cardiothoracic ratio bore no relation to the LV–Ao pressure difference. The cardiothoracic ratios were also compared with the assessment of physical signs. In patients over 21 years of age the mean cardiothoracic ratio was slightly higher in those judged severe than in those judged moderate (50·5% vs 46·6%, $p < 0.05$) but no other significant relations were observed.

The correlation between the LV–Ao pressure difference and the calculated aortic valve area index was relatively weak (Fig. 4, $r = 0.576$ by simple regression). The aortic valve area index did not correlate as well as the LV–Ao pressure difference with the physical assessment of AS or the electrocardiographic assessment of left ventricular hypertrophy. Other catheterisation data are summarised in Table 2.

Table 2 *Cardiac catheterisation data*

	Clinical assessment of aortic stenosis		
	Mild	*Moderate*	*Severe*
LV–Ao pressure difference (mmHg)	20 ±11	50 ±15	90 ±28
Cardiac index (l/min per m^2)	4·4 ±2·4	4·1 ±1·4	4·0 ±1·3
Aortic valve area index (cm^2/m^2)	—	0·52 ±0·15	0·38 ±0·15
LVEDP (mmHg)	7·5 ±4·3	8·7 ±5·9	9·2 ±6·6

Values given are mean ±1 standard deviation.
Significance of differences:

LV–Ao pressure difference:	mild vs moderate	$p < 0.001$
	moderate vs severe	$p < 0.001$
Aortic valve area index:	moderate vs severe	$p < 0.05$

Other differences were not significant. 1 mmHg = 0·133 kPa.

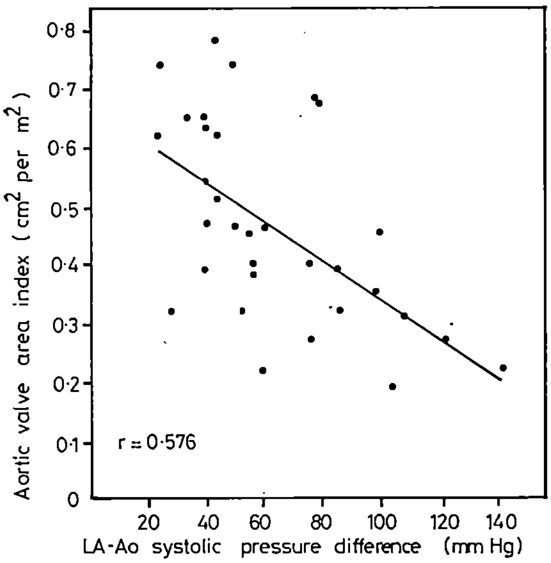

Fig. 4 *Relation between peak LV–Ao pressure difference and aortic valve area index. There is a wide scatter of values.*

FOLLOW-UP DATA

Fig. 5 shows the cumulative actuarial curves[27] for the 153 patients who presented with mild AS. One patient died in this group (case 1, Table 3). Fifty-five per cent of the patients remained with mild AS after 18 years but the remainder developed a more severe lesion, judged sufficiently important to warrant operation in 23 per cent.

Fig. 6 shows the cumulative actuarial curves for the 54 patients presenting with moderate AS. Two patients died in this group (cases 2 and 3, Table 3). Forty-two per cent of the group remained with moderate AS after 15 years but the remainder developed a more severe lesion, and 42 per cent underwent operation.

Eleven patients with a mean age of 12·6 years presented with severe AS and had an operation within 12 months of presentation.

The mean age of presentation in the 44 patients who had an operation was 10 years (1 to 25 years) and the mean age at the time of operation was 14·2 years (1 to 35 years). There were 30 male and 14 female patients. Before operation 25 patients had symptoms, including four with heart failure. One patient had severe AR after bacterial endocarditis and the clinical data in the remaining 43 patients are shown in Table 4. In six patients physical signs and electrocardiogram indicated only moderate AS: three of these had symptoms and had gradients of 28, 54, and 76 mmHg (3·7, 7·2, and 10·1 kPa), but

Table 3 *Deaths*

Case no.	*Deaths before operation* *Last review* *Age (y)*	*Severity*	*Death* *Age (y)*	*Cause*	*Comment*
1	4	Mild	9	Bacterial endocarditis	
2	9	Moderate AS, mild AR	18	Sudden, exercise	Lost to follow-up; lesion probably severe at death
3	24	Moderate AS, intermittent complete heart block	28	Sudden, rest	Probable Adams-Stokes attack; calcium in septum

Case no.	*Deaths after operation* *Time after operation*	*Cause*
Transventricular valvotomy		
4	Operative	
5	8 months	AR and pulmonary embolism
Transaortic valvotomy		
6	9 months	Bacterial endocarditis
7	11 years	Bacterial endocarditis on homograft inserted five years after valvotomy
8	12 years	Lost to follow-up; severe AS
9	12 years	Myocardial infarction; left coronary artery occluded, moderate AS
Homograft replacement		
10	7 years	Reoperation for homograft failure

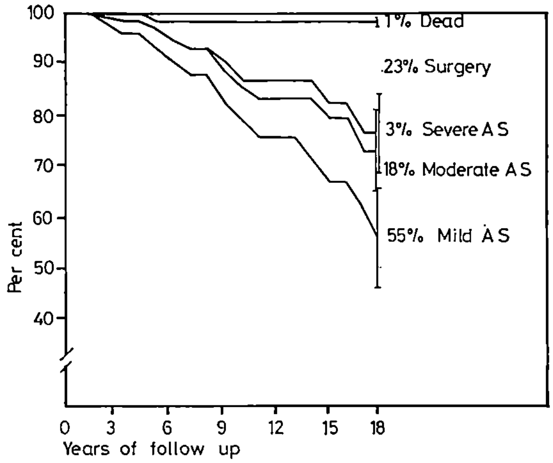

Fig. 5 *Cumulative actuarial curves of 153 patients presenting with mild aortic stenosis. The actuarial curves are plotted to the point where the smallest subgroup has 10 members at risk. Bars show ±1 standard error at this point. Mean age at presentation, 6·5 years (range 1 to 25 years); mean follow-up, 8·8 years (range 1 to 26 years).*

the clinical status of the first patient was probably misjudged; in the three without symptoms the gradient was not measured in two and in the other was 98 mmHg (13·0 kPa). All six had a valvotomy though two would not require operation by our current criteria; one has mild AS 17 years later and the other moderate AS/AR 17 years later.

Four patients had a transventricular aortic valvotomy. There was one operative death and one late death (cases 4 and 5, Table 3), one patient had severe AR 22 years after operation, and one patient has mild AS 10 years after operation.

The mean age at presentation in the 30 patients who had a transaortic valvotomy was 8·8 years (1 to 25 years) and the mean age at the time of operation was 12·1 years (2 to 30 years). Fig. 7 shows the cumulative actuarial curve for this group, the mean follow-up period being 13 years. There were no operative deaths but there have been four late deaths (cases 6 to 9, Table 3). Ten patients required later aortic valve replacement. The reason for reoperation was recurrent AS in seven patients and severe AR in three. The mean time between aortic valvotomy and aortic valve replacement was 9·1 years (range of four to 14 years). There were no hospital deaths after reoperation but there was one late death (case 7, Table 3). Of the 17 other surviving patients, eight have a significant residual lesion: four have moderate AS and four moderate AS/AR. The development of significant AR after valvotomy was unrelated to the number of valve cusps, occurring in three of 10 with a tricuspid valve and in five of 19 with a bicuspid valve, but not in the one patient with a unicuspid valve.

One patient had an exploration of the aortic valve with a view to aortic valvotomy which was judged impractical on direct inspection. Preoperatively the pressure gradient was only 40 mmHg (5·3 kPa) but the electrocardiogram showed severe

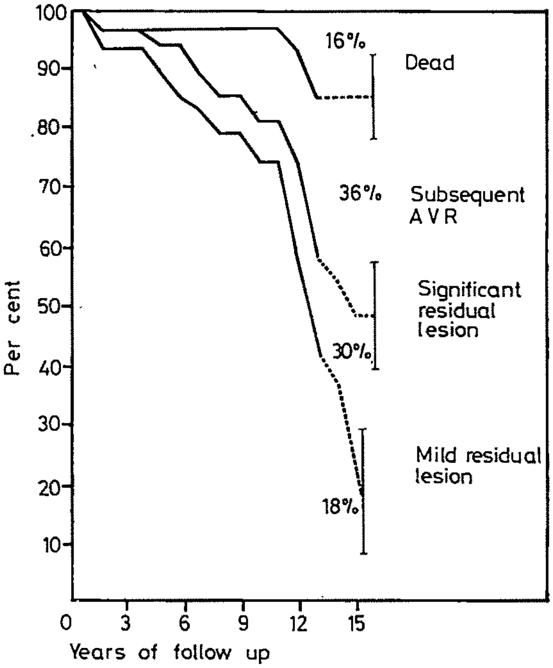

Fig. 7 *Cumulative actuarial curves of 30 patients undergoing transaortic valvotomy. Conventions as in Fig. 5 In the period from 13 to 15 years* (dotted curves) *eight patients were at risk in the smallest subgroup.*

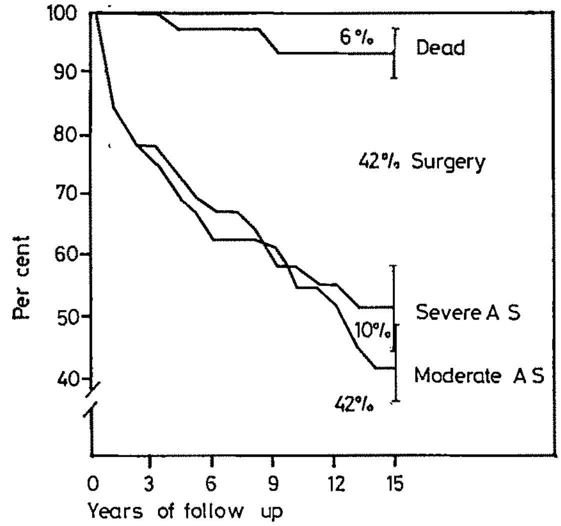

Fig. 6 *Cumulative actuarial curves of 54 patients presenting with moderate aortic stenosis. Conventions as in Fig. 5. Mean age at presentation, 11·8 years (range 1 to 25 years). Mean follow-up, 8·5 years (range 1 to 24 years).*

Table 4 *Preoperative findings in 43 surgical patients**

25 Patients with symptoms	
Physical signs	Severe 22, moderate 3
Electrocardiographic evidence of left ventricular hypertrophy	Severe 16, moderate 7, mild 2
LV–Ao pressure difference (15 patients)	Range 28 to 134 mmHg mean 71 mmHg (3 below 50 mmHg)
18 Patients without symptoms	
Physical signs	Severe 11, moderate 7
Electrocardiographic evidence of left ventricular hypertrophy	Severe 6, moderate 9, mild 3
LV–Ao pressure difference (12 patients)	Range 50 to 142 mmHg mean 82 mmHg

* Excluding one with AR. 1 mmHg = 0·133 kPa.

left ventricular hypertrophy. Fifteen years later the patient has minor symptoms, the gradient is 65 mmHg, and valve replacement is planned.

Nine patients had homograft aortic valve replacement as the primary operation. The mean age at presentation was 12·5 years (6 to 23 years) and the mean age at operation was 23·6 years (14 to 35 years). Preoperatively, six patients had significant AR associated with AS, and two others had a calcified aortic valve. There were no early deaths. One patient died after a second operation for homograft failure (case 10, Table 3), one required reoperation because of endocarditis on the homograft valve, and one patient has been lost to follow-up. The other six patients are alive and well.

Table 5 lists the significant postoperative complications which occurred in the patients having aortic valvotomy or homograft aortic valve replacement.

In 24 patients who had satisfactory operations, follow-up electrocardiograms were available at a time when the residual aortic lesion was judged trivial or mild. A comparison of pre- and postoperative electrocardiograms in this group is shown in Table 6. Most patients showed improvement in the electrocardiogram and in two-thirds this was sufficient to move them at least one grade in the arbitrary classification.

BACTERIAL ENDOCARDITIS

Three non-surgical patients had bacterial endocarditis, with one death. Two patients who subsequently had an operation had endocarditis before operation. From the time the patients were referred to the clinic the incidence of bacterial endocarditis without, or before surgery, was 2·7 episodes per 1000 patient years.

Table 5 *Postoperative complications in patients undergoing aortic valvotomy or primary homograft aortic valve replacement*

Complications	*Aortic valvotomy (30)*	*Homograft aortic valve replacement (9)*
Wound infection	3	0
False aneurysm of femoral artery at site of cannulation	2	0
Myocardial damage (new Q waves)	0	2
Haemorrhage	1	1
Postcardiotomy syndrome	1	0
Cerebral embolism with recovery	2	0
Ventricular tachycardia	1	0
Reoperation for malpositioned aortic homograft	0	1
Total number of patients with complications	8	3

Table 6 *Comparison of degree of left ventricular hypertrophy in pre- and postoperative electrocardiograms in 24 patients with trivial or mild residual lesion**

Left ventricular hypertrophy in initial electrocardiogram		*Left ventricular hypertrophy in follow-up electrocardiogram*			
		None	*Mild*	*Moderate*	*Severe*
Severe	13	5	1	4	3
Moderate	7	3	2	2	
Mild	4	1	3		

* Duration of follow-up 20 to 173 months (mean 96).
Figures given are the numbers of patients in each category.

Four patients had bacterial endocarditis postoperatively, one after valvotomy (2·8 episodes per 1000 patient years) and three after homograft aortic valve replacement (34 episodes per 1000 patient years), one of the latter having also had an attack before operation. This, presumably by chance, is higher than the average incidence for endocarditis on homograft valves in this hospital, which is 57 episodes in 5274 patient years, or 10·8 per 1000 patient years. The overall postoperative incidence in the present study was 8·9 episodes per 1000 patient years. Numbers are too small for statistical assessment.

Discussion

This study was arbitrarily restricted to patients presenting between the ages of 1 and 25 years to provide a relatively uniform group. There are special problems associated with aortic stenosis in neonates, and patients who present after the age of 25 usually do so with calcific aortic stenosis. The group of 2000 patients with a systolic murmur may include several hundred patients with trivial AS whose prognosis is almost certainly better than that of the study group. This study, therefore, describes the progress of 218 patients with typical signs of valvar AS; it is possible that a few patients with membranous subaortic stenosis have been included with those who have had neither cardiac catheterisation nor operation but this should not materially affect the conclusions.

RELIABILITY OF PHYSICAL SIGNS

Dyspnoea, angina, or syncope usually indicate a severe lesion,[8 28] and in our series 85 per cent of the 31 patients with symptoms were judged at that time to have a severe lesion. The development of symptoms is, however, influenced by factors other than the severity of obstruction, and only 26 of 56 patients with a severe lesion had symptoms.

The intensity of the systolic murmur, the presence of a thrill, an apical fourth heart sound, and a thrusting left ventricular impulse are typical of AS but do not reliably predict the severity of the obstruction. Several authors have investigated the relation between the LV-Ao pressure difference and the pulse pressure, the character of the pulse, and the second heart sound. Both Peckham *et al.*,[19] and Glew *et al.*[8] comment on the usefulness of a small pulse pressure as an indication of moderate or severe AS. We have used a subjective impression of the pulse volume and contour at a large artery, usually the brachial artery. Correlation with measured pulse pressure is not exact but the reduced pulse pressure probably contributes to the impression of an altered pulse contour. Beyond the infant age group detection of an altered pulse contour in a large artery is remarkably reproducible, and Eddleman *et al.*[15] showed that a slow carotid upstroke was the best of the factors they analysed in predicting an LV–Ao pressure difference of 50 mmHg (6·7 kPa) or more.

Braunwald *et al.*[5] found that the mean LV–Ao pressure difference in patients with a single second sound on phonocardiography was 100 mmHg (13·3 kPa) and in patients with a narrowly split second sound was 49 mmHg (6·5 kPa). We have not used phonocardiography on a regular basis but have found that assessment of the second heart sound is generally reproducible between experienced observers. Difficulties resulting from conduction anomalies or heavily calcified valves rarely arise in patients of the age group in this study.

Most of the authors who criticise the accuracy of physical signs studied a mixed group of patients; for example, the group of Braunwald *et al.*[5] included 20 per cent with other lesions (12% with shunts). Concentration on a single sign further limits the sensitivity of clinical assessment. In the absence of any complicating factor we have taken a minor or pronounced abnormality of any one sign as an indication of moderate or severe stenosis, respectively. When comparisons were made with LV–Ao pressure differences there was, as expected, some overlap between the mild and moderate and between the moderate and severe groups, but not between the mild and severe groups (Fig. 1). Excluding those with severe AR, patients with lesions judged mild had an LV–Ao pressure difference less than 40 mmHg (5·3 kPa) and those with lesions judged severe had a gradient greater than 55 mmHg (7·3 kPa). Some of the overlap seen is to be expected when gradients are compared without taking account of variations in cardiac output, and the use of calculated aortic valve area has great theoretical appeal. The number of patients in the present series with valve area calculations is relatively small (Fig. 4), but, like Miettinen and Rees,[29] we were disappointed to find no practical advantage in the use of valve areas; the correlations with clinical and electrocardiographic assessments were less good with valve area than with LV–Ao pressure difference.

Many authors have commented that important AS can occur with a normal electrocardiogram, and our study confirms this, bearing in mind that many electrocardiograms were graded as showing mild left ventricular hypertrophy on voltage criteria which overlap the normal range in this age group. On the other hand, Hohn *et al.*[14] reported an abnormal electrocardiogram in 79 per cent of patients with an LV–Ao pressure difference greater than 50 mmHg (6·7 kPa) and in 90 per cent of patients with a pressure difference greater than 77 mmHg (10·3 kPa). In our series, 37 of 47 patients with a pressure difference greater than 50 mmHg (6·7 kPa) had moderate or severe left ventricular hypertrophy as did 16 of 18 with a pressure difference greater than 75 mmHg (10·0 kPa). We deliberately kept the voltage criteria for moderate left ventricular hypertrophy strict: 75 per cent of patients classified as having moderate left ventricular hypertrophy fell into this category because of ST and T wave abnormalities, and the voltage evidence in the remainder was very impressive. Surprisingly, inclusion of the electrocardiogram in the clinical assessment did not improve the correlation with LV–Ao pressure differences (Fig. 3). Nevertheless, the development of ST and T wave changes in the electrocardiogram is important, probably representing relative impairment of subendocardial coronary blood flow. In patients with important AS such electrocardiographic changes can be produced by exercise, making the exercise electrocardiogram a more sensitive test.[30–32] It is significant that the indirect assessment of the adequacy of coronary perfusion (DPTI/SPTI) was found to be related to the electrocardiographic change,[33] and a slightly modified version of this index correlated well with symptoms.[34] The presence of ST and T wave changes in the electrocardiogram can, therefore, usually be taken as an indication of severe obstruction, though there are exceptions as shown by our patient who remained well 15 years after exploration of his aortic valve. Not surprisingly, plain chest *x*-rays made no significant contribution to the assessment of severity.

We conclude that assessment of symptoms, physical findings, and the electrocardiogram provides information which is sufficiently accurate to determine management in most cases. We have little experience with other non-invasive methods using systolic time intervals, analysis of the carotid upstroke, vectorcardiography, and apex cardiography,[1–3 13] but question whether they add materially to the precision of assessment. Newer techniques in radiology,[35] M-mode echocardiography,[36 37] or cross-sectional echocardiography,[38] may well do so, but whether or not they will enter general clinical use remains to be seen.

RISK OF SUDDEN DEATH

The main reason for requiring accurate assessment is the risk of sudden death, a subject emphasised repeatedly in the published reports. The incidence of sudden death in AS has varied in different reports according to selection but is probably in the region of 1 per cent.[20 21] In the collaborative study of Lambert *et al.*[39] all patients who died suddenly had severe left ventricular hypertrophy on the electrocardiogram. After reviewing published data, Doyle *et al.*[28] concluded that sudden death in the absence of severe electrocardiographic abnormalities and/or symptoms is very uncommon. Of the 10 patients in our series who died, death was attributable directly to aortic stenosis in only two (cases 2 and 8, Table 3), both of whom had been lost to follow-up for many years.

Table 7 shows those published cases of sudden death without ST and T wave changes: it is clear that sudden death in patients with no symptoms and normal physical findings has not been documented. The risk of sudden death, directly attributable to AS, is virtually limited to those patients with a severe lesion. We have already given our reasons for believing that physical findings provide a reliable indication of an important obstruction even when the electrocardiogram is normal. For these reasons we regard careful clinical assessment as adequate protection against the catastrophe of sudden death and do not accept the need for routine cardiac catheterisation recommended by others.[9–11]

INDICATIONS FOR OPERATION

In deciding the indications for operation, it must be borne in mind that aortic valvotomy is no panacea. In Table 8 we have summarised a number of published results. As far as possible, we have extracted data to include only patients who had valvar AS and who were over the age of 1 year. Overall, the early operative mortality is low but late mortality is greater and, to some extent, dependent upon the length of follow-up. Furthermore, bacterial endocarditis, the redevelopment of significant aortic valve lesions, and reoperation occur with increasing frequency. About 75 per cent of our patients had a mild residual lesion at 10 years but from this time there was a dramatic increase in the number of patients who either required reoperation or had an important residual lesion (Fig. 7). Sudden death still occurred despite valvotomy though some cases were avoidable

Table 7 *Summary of patients with normal ST segments and T waves who died suddenly*†

Author	*Case no.*	*Age (y)*	*Symptoms*	*Pulse volume*	*Pulse character*	*Second sound*	*Electrocardiogram*	*Catheterisation*	*Activity at death*
Braverman and Gibson[17]	1	4	Syncope, dyspnoea	NS	NS	NS	Normal (10 mth before death)	—	Sleeping
	2	9	Fatigue	BP 84/60	NS	NS	WPW (2¾ y before death)	—	Standing
Reynolds *et al.*[40]	3	4	Syncope, heart failure	BP 80/60	NS	NS	Mild LVH* (2 wk before death)	—	Resting in bed
Landtman *et al.*[41]	4	10	Dyspnoea (for 5 y)	NS	NS	NS	LVH (time before death NS)	—	NS
Campbell[20]	5	12	Angina, syncope, dyspnoea	NS	NS	NS	Mild LVH* (4 mth before death)	36 mmHg LV-Ao pressure difference 6 y before death	Walking
Glew *et al.*[8]	5	2 3/12	Syncope	Normal	NS	NS	Mild LVH* (2 wk before death)	—	NS
Reid *et al.*[42]	7	8	Nil	NS	NS	NS	Mild LVH (time before death NS)	—	Football
	8	15	Nil	NS	NS	NS	Mild LVH (time before death NS)	—	Swimming
Wagner *et al.*[12]	9	16	NS	NS	NS	NS	NS (presumably no T wave changes at time of catheterisation)	68 mmHg LV-Ao pressure difference 17 mth before death	Basketball

NS, not stated.

* We have used our criteria for left ventricular hypertrophy where records are available.

† Three cases listed by Doyle *et al.*[28] have not been included because one had subvalvar AS, one died of a ruptured subclavian aneurysm, and one had left bundle-branch block with signs of severe aortic stenosis.

emphasising the need for meticulous follow-up of patients both before and after operation. There was no evidence that the incidence of bacterial endocarditis was reduced by operation. On the contrary, the findings are compatible with the suggestion of Gersony and Hayes[49] that the incidence may be increased.

Although this is frequently recommended,[22–26] we can find no justification either in our data or in other published reports for advising valvotomy simply because the LV–Ao gradient is greater than 50 mmHg (6·7 kPa). It is at approximately this level that symptoms develop in some patients, the lesion begins to appear important on physical signs, and ST depression or T inversion may appear, but, on the other hand, many patients show none of these features and tolerate obstruction of this severity for long periods. Wagner *et al.*[12] presented data which suggested that results with surgical treatment were better than results with medical treatment in patients with a gradient of 50 to 79 mmHg (6·7 to 10·5 kPa): one surgical patient and four medical patients died. The significance of this is, however, doubtful, as three surgical patients and one medical patient whose gradients fell just outside this range also died. It is disappointing that the use of valve area does not provide a clearer criterion for recommending operation. This is no doubt partly the result of errors in measurement, but we believe that it is also partly because of a variation in effective valve area dependent on the strength of contraction of the left ventricle at the time of measurement. Fortunately, very low cardiac outputs are unusual at the time of study in this age group so that a gross underestimate of severity is not common. By contrast, an overactive circulation is not uncommon and the LV–Ao gradient on its own quite frequently gives an exaggerated impression of severity. Other methods of assessment of the severity of the lesion based on oxygen requirements[34] have not so far provided a clearer cut-off point.

We do not recommend operation for patients who are free from symptoms and who do not show at least moderate changes in the pulse, second heart sound, or electrocardiogram, even though there are many such patients with an LV–Ao pressure difference greater than 50 mmHg. Dyspnoea,

Table 8 *Results of aortic valvotomy in published reports*

Author	*No. of patients*	*Mean length of follow-up (range)*	*Early mortality*	*Late mortality*	*Reoperation rate*	*Significant AR*	*Significant AS*	*Endo-carditis*	*Good result*
Spencer *et al.*[43]	8	NS (1–6 mth)	0	0	NS	25%	12·5%*	0	NS
Lees *et al.*[44]	26	17 mth (9 mth to 3½ y)	4%	0	NS	4%	29% (2 of 7 studied)	0	NS
Ellis *et al.*[23]	33	18 mth (6–39 mth)	6%	6%	NS	18%	NS	3%	67%
Morrow *et al.*[22]	27	9 mth† (2½–17 mth)	10%	0	NS	14%	7%	NS	NS
Cooley *et al.*[24]	55	NS (1–8 y)	1·8%	NS	NS	NS	NS	NS	NS
Thomson and Fisher[45]	23	3·4 y (1–6 y)	0	4%	4%	22%	4%	NS	74%
Fisher *et al.*[46]	26	18 mth† (6 mth to 5 y)	0	4%	NS	8%	20%	NS	68%
Shackleton *et al.*[47]	25	7·5 y (3–10 y)	4%	8%	8%	20%	NS	NS	NS
Bernhard *et al.*[25]	116	NS (1–15 y)	2·5%	5%	10%	43%	14%	1%	NS
Conkle *et al.*[26]	38	10 y (5–14 y)	0	2·5%	8%	10%	16%	10%	69%
Jack and Kelly[48]	42 (>2 y of age, 5 lost to follow-up)	10·6 y (6–16·3 y)	0	8%	11% (recommended in 27%)	25%	40% (6 of 15 studied pre- and postop)	5·5%	56%
Wagner *et al.*[12]	162 (>2 y of age)	6·5 y† (3–9 y)	1·2%	2·4%	NS	4·7%	34·6%	NS	35% (45 of 127)
Present data	30	13 y (1-17y)	0	13%	33%	27%	40%‡	7%	30%

* LV-Ao pressure difference estimated at operation. † Time of catheterisation. ‡ Assessed clinically. NS, not stated.
Data include only patients with valvar aortic stenosis who were older than 1 year of age. Non-cardiac deaths have been excluded from late mortality. Significant aortic regurgitation is defined as pulse pressure greater than 50 mmHg; some of the difference between series is a result of different methods of data presentation. Significant aortic stenosis is defined as peak LV-Ao pressure difference of 50 mmHg or greater. A good result is an asymptomatic patient who has mild aortic stenosis or mild aortic regurgitation.

confidently attributed to the cardiac lesion, indicates moderate or severe obstruction but, where other findings are compatible with a moderate lesion only, dyspnoea occurs only with strenuous exertion, and the patient can avoid extremes of exertion without seriously interfering with his lifestyle, we believe it reasonable to continue careful observation. On the other hand, syncope or angina indicates a severe lesion, almost always an indication for operation. The reason why one patient develops symptoms and another with a seemingly identical lesion does not is presumably related to the habitual level of physical exercise, the personality of the individual and his level of autonomic responsiveness, and probably to the physical characteristics of the pulmonary vascular bed. Some patients with signs of a severe lesion have no symptoms and, provided that extremes of exercise are avoided, continued observation is permissible until such time as the electrocardiogram begins to show significant ST depression or T inversion. Even then long survival is possible, as shown by the presentation of patients late in life with calcific AS, some of whom have probably maintained this situation for decades. Furthermore, ST and T wave changes, at least those of moderate degree, will usually regress after a satisfactory operation (Table 6). Nevertheless, the low mortality and morbidity of aortic valvotomy, the risk of sudden death, and the likelihood of progressive myocardial impairment with long-term subendocardial ischaemia are sufficient reasons for recommending valvotomy in the presence of these electrocardiographic changes. We have not accepted that routine preoperative cardiac catheterisation is mandatory but in practice have investigated many patients to add to the precision of assessment, particularly when there is any discrepancy between symptoms, physical signs, and the electrocardiogram. In older patients, coronary arteriography is also desirable. Though we have not accepted any LV–Ao pressure difference as an absolute indication for operation, in practice a gradient of 75 or 80 mmHg (10·0 or 10·6 kPa) is usually associated with symptoms if the patient leads an active life and with clinical signs of severe obstruction including, sooner or later, ST or T wave changes on the electrocardiogram.

The criteria for recommending operation amount to the presence of physical signs of moderate or severe obstruction, combined either with significant symptoms or with pathological ST and T wave changes on the electrocardiogram. With the few exceptions described earlier, these criteria have been used during the period of this study. With these criteria, the risk of sudden death is minimal and irreversible myocardial changes are unlikely to occur. In a patient who is probably faced with several operations in his lifetime, we do not believe surgical intervention warranted until these criteria are fulfilled. If it could be shown that early valvotomy slowed the progression of thickening and calcification of the valve, more liberal criteria for operation would be appropriate, but we know of no such evidence and doubt if the proportion of patients benefiting from this would be sufficient to justify early operation as a routine. Though cineangiographic assessment of the valve has improved in recent years, it is still not possible, in our hands, to predict those patients in whom an excellent result will be obtained. However, the risk of producing significant AR has diminished over the years. Earlier reports suggested that AR developed most frequently when an inappropriate attempt was made to render the valve tricuspid,[22 45] but our series shows no relation between anatomy and the development of AR. Though this risk is now small we do not at present feel that attempted valvotomy is warranted unless the lesion is severe enough to justify valve replacement should the anatomy be unfavourable.

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Br Heart J 1980; **43**: 574–8

Relation between caval and pulmonary artery oxygen saturation in children

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SUMMARY The flow relation between that in the superior vena cava and inferior vena cava was studied in order to estimate the oxygen saturation of mixed venous blood in connection with heart catheterisation of children between the ages of 5 and 8 years without cardiac shunts. The investigation includes a group of 19 children examined during halothane anaesthesia and a group of 40 examined under local anaesthesia. The groups were comparable in respect of age and body surface. The results show that the oxygen saturation of mixed venous blood (MVB) is higher under general anaesthesia than during local anaesthesia, and that the oxygen saturation in the former group is highest in the superior vena cava (SVC) and lowest in the inferior vena cava (IVC), while the reverse is the case during examination under local anaesthesia. Based on multiple regression analysis, it is advisable, for children between the ages of 5 and 8 years, to use the formula $MVB_{calc} = -0{\cdot}85 + 0{\cdot}81\ SVC + 0{\cdot}18\ IVC$ for the estimation of the oxygen saturation in the mixed venous blood in children under general anaesthesia and the formula $MVB_{calc} = 10{\cdot}21 + 0{\cdot}52\ SVC + 0{\cdot}34\ IVC$ for children during local anaesthesia.

When estimating mixed venous blood in younger children and during general anaesthesia or both, more emphasis should be laid on the flow through the superior vena cava.

Calculation of the oxygen saturation of mixed venous blood is essential for the determination of the systemic cardiac output, when employing the Fick principle in patients with cardiac shunts.

The mixed venous blood depends on the flow and oxygen saturation in the superior vena cava, the inferior vena cava, and the coronary sinus. A total admixture of the blood streams from these three areas is first obtained in the pulmonary artery.[1] No attention is paid to the influence of the flow from the coronary sinus during routine catheterisation, and for this reason the practical basis for the calculation of mixed venous blood normally only includes the flow in the two caval veins.

This basis for the calculation appears to differ in children subjected to examination under general anaesthesia from that in adults examined under local anaesthesia. In children between birth and 3 years without an intracardial shunt and examined under general anaesthesia, Thomsen[2] found the best correlation between the mixed venous blood (MVB) measured directly (MVB_{meas}) and MVB calculated (MVB_{calc}) when using the formula:

$$MVB_{calc} = \frac{3\ SVC + IVC}{4}$$

where the superior vena cava (SVC) and inferior vena cava (IVC) are the oxygen saturation in the superior and inferior caval veins, respectively. Miller *et al.*[3] were unable to find a satisfactory formula for the calculation of mixed venous blood in children between birth and 10 years, examined under general anaesthesia.

The present investigation differs considerably in respect of both the type of anaesthesia and the age of the children. No previous report has included a reference group consisting entirely of children examined under local anaesthesia. In adults examined under local anaesthesia, the best correlation between MVB_{meas} and MVB_{calc} has been obtained using the formulae:

$$MVB_{calc} = \frac{SVC + IVC}{2}$$

(Nielsen and Fabricius)[4] and

Received for publication 8 October 1979

$$\mathrm{MVB}_{\mathrm{calc}} = \frac{3\ \mathrm{SVC} + \mathrm{IVC}}{4}$$

(Flamm *et al.*[5]).

The present retrospective study has been carried out in order to find the most suitable formula for the calculation of mixed venous blood in children.

Patients and methods

The material consists of 59 heart catheterisations of children in which the following criteria were complied with: (1) age between 60 and 96 months; (2) mixed venous blood between superior vena cava and inferior vena cava; and (3) no cardiac shunts.

Criterion (2) has been included partly in order to ensure that gross errors of method do not occur and partly to permit the estimation of the flow distribution between the superior and inferior caval veins.

Nineteen catheterisations were carried out under general anaesthesia (group A). All were performed under N_2O-O_2-halothane anaesthesia, with the patient on spontaneous respiration. The oxygen content of the inspired air was between 33 and 50 per cent. The anaesthetics were supplemented with local infiltration of lignocaine 1 per cent in order to obtain light anaesthesia.

Forty catheterisations were carried out under local anaesthesia with lignocaine 1 per cent (group B). This was performed as an infiltration anaesthesia around the vein employed and only in five cases was it necessary to supplement this with intravenous pethidine.

The cardiac diagnoses in the two groups are shown in Table 1. The average age of the patients in group A was 74 months and the average surface area 0·84 m^2. In group B the corresponding figures were 81 months and 0·88 m^2.

The blood samples were withdrawn, as is the routine in the department, from the superior and inferior caval veins just before entering the right atrium (high IVC) and in the trunk of the pulmonary artery (MVB).

Table 1 *Distribution of diagnoses among groups under general (A) and local (B) anaesthesia*

Diagnosis	*Group A*	*Group B*
Normal	5	24
Aortic stenosis	4	6
Pulmonary stenosis	3	7
Operated heart disease	4	2
Aortic coarctation (mild)	2	1
Mitral regurgitation	1	—
Total	19	40

The oxygen saturation determinations were carried out by reflection-photometry ("Oximeter"—Elema-Schønander).

Calculation of the flow distribution between the superior and inferior caval veins was based on the following formula:

$$\frac{\dot{Q}_{\mathrm{SVC}}}{\dot{Q}_{\mathrm{IVC}}} = \frac{\mathrm{MVB} - \mathrm{IVC}}{\mathrm{SVC} - \mathrm{MVB}}$$

where MVB, SVC, and IVC are the mean oxygen saturations in the trunk of the pulmonary artery, superior vena cava, and inferior vena cava, respectively.

Mixed venous blood was calculated using the following formulae:

(a) $\mathrm{MVB}_{\mathrm{calc}} = \mathrm{SVC}$

(b) $\mathrm{MVB}_{\mathrm{calc}} = \dfrac{\mathrm{SVC} + \mathrm{IVC}}{2}$

(c) $\mathrm{MVB}_{\mathrm{calc}} = \dfrac{3\ \mathrm{SVC} + \mathrm{IVC}}{4}$

(d) $\mathrm{MVB}_{\mathrm{calc}} = \dfrac{2\ \mathrm{SVC} + \mathrm{IVC}}{3}$

(e) $\mathrm{MVB}_{\mathrm{calc}} = \dfrac{3\ \mathrm{SVC} + 2\ \mathrm{IVC}}{5}$

(f) $\mathrm{MVB}_{\mathrm{calc}} = -0{\cdot}85 + 0{\cdot}81\ \mathrm{SVC} + 0{\cdot}18\ \mathrm{IVC}$

(g) $\mathrm{MVB}_{\mathrm{calc}} = 10{\cdot}21 + 0{\cdot}52\ \mathrm{SVC} + 0{\cdot}34\ \mathrm{IVC}$

Formulae (a), (b), and (c) have been previously used.

Formulae (d) and (e) have been worked out from the theoretical relation between the flows in the superior and inferior vena cavae in groups A and B, respectively; an attempt has been made to use whole coefficient. Formulae (f) and (g) have been arrived at by multiple linear regression analysis of the measured values in groups A and B, respectively. A comparison between $\mathrm{MVB}_{\mathrm{meas}}$ and $\mathrm{MVB}_{\mathrm{calc}}$ within the individual groups was carried out partly by means of linear regression analysis and partly using difference determinations. The regressions obtained in this manner were statistically analysed, with regard to a significant difference from the line of identity at a 5 per cent significance level. The mean values, mean differences, intercept, and slope have been compared using Student's t test.

Results

GROUP A

A significant correlation was found by means of linear regression analysis between mixed venous blood and superior vena cava ($r = 0{\cdot}90$, $p < 0{\cdot}001$) and inferior vena cava ($r = 0{\cdot}57$, $p < 0{\cdot}005$), respectively, while no significant correlation could be found between mixed venous blood and age ($r = -0{\cdot}18$) or surface area ($r = 0{\cdot}12$). Formula (f) was obtained by means of multiple regression analysis of the measured oxygen saturations in mixed venous blood, superior vena cava, and inferior vena cava, respectively.

Table 2 shows the mean values and scatter of mixed venous blood, superior vena cava, and inferior vena cava. The superior vena cava values are significantly higher than those of the inferior vena cava ($p < 0{\cdot}001$). The relation between flows in the superior and inferior caval veins were calculated as 2·0, using these mean values.

Table 2 *Mean values ±1 SD of oxygen saturation in mixed venous blood (MVB), superior vena cava (SVC), and inferior vena cava (IVC)*

	Group A	*Group B*	*Probability*
MVB	83·0 ±4·0	75·9 ±3·5	< 0·001
SVC	87·2 ±3·9	73·8 ±4·1	< 0·001
IVC	74·4 ±6·6	79·3 ±5·7	< 0·01

Table 3 shows the regression indices with the comparison of the measured and calculated values of mixed venous blood, when using formulae (a) to (f). In addition, the mean difference between the measured and calculated values is shown.

By inserting the values from group B for superior vena cava and inferior vena cava into formula (f) a linear regression was found between $\mathrm{MVB}_{\mathrm{calc}}$ and $\mathrm{MVB}_{\mathrm{meas}}$ which was significantly different from the lines of identity and also different from the linear regression obtained by using the measured values for SVC and IVC from group A in formula (f). The mean differences in both cases differed from zero ($p < 0{\cdot}001$).

GROUP B

A significant correlation was found by means of linear regression analysis between mixed venous blood and superior vena cava ($r = 0{\cdot}75$, $p < 0{\cdot}001$) and inferior vena cava ($r = 0{\cdot}72$, $p < 0{\cdot}001$), respectively, while no significant correlation could be shown between mixed venous blood and age ($r = 0{\cdot}15$) or surface area ($r = 0{\cdot}17$). The previously mentioned formula (g) was derived from multiple regression analysis of the measured oxygen saturations in mixed venous blood, superior vena cava, and inferior vena cava.

The mean values and scatter of mixed venous blood, superior vena cava, and inferior vena cava are shown in Table 2. The values of the inferior vena cava are significantly higher than those of the superior vena cava ($p < 0{\cdot}001$). The relation between flow in the superior and inferior vena cavae was calculated as 1·6 using these mean values of oxygen saturation.

Table 4 shows the regression indices with the comparison between measured and calculated values of mixed venous blood using formulae (a) to (e) and (g). In addition, the mean difference between the measured and calculated values is shown.

Discussion

The present investigation shows that the significantly highest values were obtained for mixed

Table 3 *Formulae used with respective regression indices ±1 SD in group A (19 patients)* ($\mathit{MVB}_{\mathit{meas}} = a + b \times \mathit{MVB}_{\mathit{calc}}$)

Formula	*Intercept*	*Slope*	*Syx*	*r*	*Mean difference*
(a) $\mathrm{MVB} = \mathrm{SVC}$	3·5 ±9·3	0·91 ±0·11	1·8	0·90	−4·2 ±1·8*
(b) $\mathrm{MVB} = \dfrac{\mathrm{SVC} + \mathrm{IVC}}{2}$	20·7 ±10·4	0·77 ±0·13	2·3	0·82	2·0 ±2·5*
(c) $\mathrm{MVB} = \dfrac{3\,\mathrm{SVC} + \mathrm{IVC}}{4}$	2·6 ±7·2	0·96 ±0·09	1·4	0·94	−1·1 ±1·4*
(d) $\mathrm{MVB} = \dfrac{2\,\mathrm{SVC} + \mathrm{IVC}}{3}$	8·6 ±8·2	0·90 ±0·10	1·7	0·91	0·0 ±1·7
(e) $\mathrm{MVB} = \dfrac{3\,\mathrm{SVC} + 2\,\mathrm{IVC}}{5}$	11·0 ±9·3	0·88 ±0·11	1·9	0·88	0·9 ±1·9
(f) $\mathrm{MVB} = -0{\cdot}85 + 0{\cdot}81\,\mathrm{SVC} + 0{\cdot}18\,\mathrm{IVC}$	1·5 ±6·9	0·98 ±0·08	1·3	0·94	−0·1 ±1·3

* $p < 0{\cdot}05$ compared with line of identity.

Table 4 *Formulae used with respective regression indices ±1 SD in group B (40 patients)* ($MVB_{meas} = a + b \times MVB_{calc}$)

Formula	Intercept	Slope	Syx	r	Mean difference
(a) $MVB = SVC$	32·5 ±6·5*	0·59 ±0·09*	2·4	0·73	1·9 ±3·0*
(b) $MVB = \frac{SVC + IVC}{2}$	14·0 ±4·3*	0·81 ±0·06*	1·4	0·92	−0·8 ±1·6*
(c) $MVB = \frac{3\,SVC + IVC}{4}$	10·1 ±5·3	0·87 ±0·07	1·6	0·90	0·6 ±1·6*
(d) $MVB = \frac{2\,SVC + IVC}{3}$	10·2 ±4·7*	0·87 ±0·06*	1·4	0·91	0·4 ±1·5
(e) $MVB = \frac{3\,SVC + 2\,IVC}{5}$	10·4 ±4·2*	0·86 ±0·06*	1·3	0·93	0·0 ±1·4
(g) $MVB = 10{\cdot}21 + 0{\cdot}52\,SVC + 0{\cdot}34\,IVC$	2·0 ±4·7	0·98 ±0·06	1·3	0·93	0·3 ±1·3

* $p < 0{\cdot}05$ compared with line of identity.

venous blood and superior vena cava, and the significantly lowest values for inferior vena cava under general anaesthesia. In addition, the inferior vena cava values are significantly higher than those of the superior vena cava under local anaesthesia, while the reverse is the case under general anaesthesia. The latter was also found by Thomsen[2] in children between the ages of 0 and 3 years, examined under corresponding anaesthetic conditions. Thus, there appears to be an alteration in the circulation in children during light general anaesthesia in such a manner that the flow through the superior vena cava is increased and that through the inferior vena cava decreased. This is supported by animal experiments,[6] which show a decreasing cerebral arteriovenous oxygen deficit in dogs under anaesthesia with rising concentrations of halothane and constant arterial P_{CO_2}. Further human investigations,[7 8] have shown a reduced oxygen saturation in the venous blood from the splanchnic area during halothane anaesthesia. It is not possible from the present retrospective investigation to determine whether the change in the flow distribution results from an effect of halothane itself or a change in arterial P_{CO_2}, or both.

The relation between the superior and inferior vena cavae and mixed venous blood in a group consisting of children only, without cardiac shunts, under local anaesthesia, does not appear to have been the object of previous reports. We found that the values for the inferior vena cava were significantly higher than for the superior vena cava. The same finding has been made in adults.[1 4 5]

The following requirements were made in order to accept satisfactory estimations of mixed venous blood by one of the previously mentioned formulae (1) that MVB_{calc} after comparison with MVB_{meas} produced a linear regression with an intercept and a slope which did not differ significantly from 0 and 1, respectively; (2) a mean difference which did not differ significantly from 0, and (3) a coefficient of correlation as near 1 as possible. The formulae which complied with these requirements were then mutually evaluated within the individual groups. We prefer the formulae with the greatest coefficient of correlation from those not mutually different.

If the coronary flow is ignored, we have found a flow relation between the superior and inferior caval veins in group A of 2·0. The formula (d) was arrived at from this value. The formulae were evaluated as described above, and in no case was the intercept found to be different from 0 or the slope different from 1. Formulae (a), (b), and (c) showed a mean difference different from 0. No significant difference could be shown between the remaining formulae (d), (e), and (f). When compared with the formula recommended by Thomsen[2] for the estimation of mixed venous blood in children examined under general anaesthesia and below the age of 3 years, we may conclude from the present investigation that one has to attribute less to the flow through the superior vena cava in older children. This may be one of the reasons why it was impossible for Miller *et al.*[3] to find a satisfactory formula, as the patients in their material were between birth and 10 years of age. Other explanations might be the type of anaesthesia and intermittent positive pressure ventilation.

Using the criteria mentioned, we found only one formula in group B which did not differ from the ideal requirements, namely formula (g). The flow relation between the superior and inferior caval veins was 1·6 in this group, and it thus appears as though the flow in the superior vena cava must be considered higher in patients under general anaesthesia. The coefficients in formula (g) can be seen to lie between the coefficients found by Nielsen and Fabricius,[4] and Flamm *et al.*,[5] respectively, in adults.

As there is no difference between the patients in the two groups in respect of surface area, it may be concluded from the present investigation that it is advisable to employ different formulae for the estimation of mixed venous blood in children between the ages of 5 and 8 years, depending on whether the cardiac catheterisation is carried out under general or local anaesthesia.

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1	NORWAY, SWEDEN & FINLAND 1968. "Medical boards' recommendations on diet in the Scandinavian countries."	✓
2	NETHERLANDS 1973. Nutrition Council: "Recommendations on the amount and nature of dietary fats."	✓
3	UNITED KINGDOM 1974. DHSS COMA Report: "Diet and coronary heart disease."	
4	GERMANY (FR) 1974. Federal health report: "Edible fats and circulatory disorders."	✓
5	UNITED KINGDOM 1976. Royal College of Phy. & the British Cardiac Soc: "Prevention of coronary heart disease."	✓
6	EUROPEAN SOCIETY OF CARDIOLOGY 1978. "Preventing coronary heart disease."	✓

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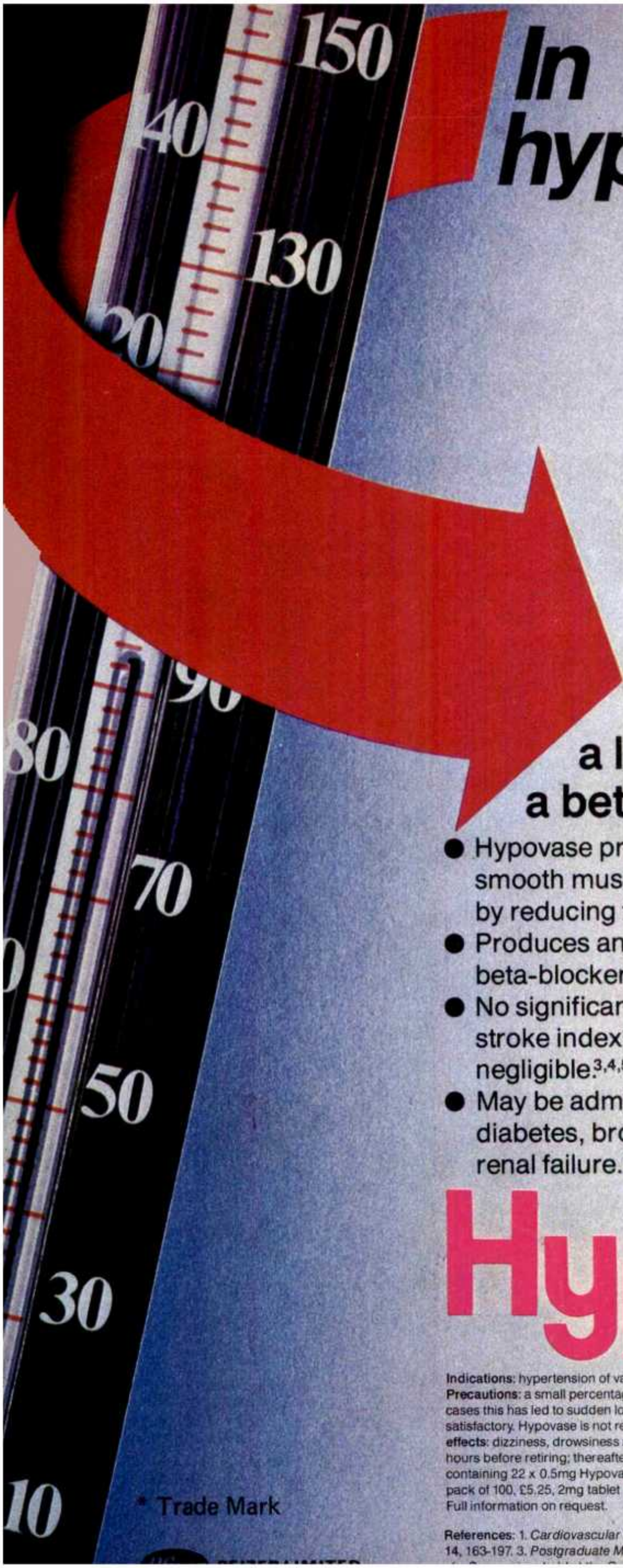

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Br Heart J 1980; **43:** 579–81

Aortic root dissection

Another cause of early systolic closure of the aortic valve

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SUMMARY An early systolic closure of the aortic valve was recorded in the echocardiogram in two patients with aortic root dissection. This sign, initially described in discrete subaortic stenosis and occasionally observed in mitral regurgitation and interventricular septal defect, has not so far been described in dissecting aneurysm of the aorta.

After the first echocardiographic description of an aortic dissection by Millward *et al.*,[1] several reports on the echocardiographic criteria[2–4] have been published.

Recently, we have studied two patients with dissecting aneurysm of the aorta which showed an echocardiographic peculiarity not so far reported: premature systolic closure of the aortic valve.

Case reports

CASE 1

A 64-year-old white woman, with a previous history of hypertension for the past nine years, was admitted to the coronary care unit because of retrosternal pain radiating toward the neck, accompanied by sweating, nausea, and vomiting, which had lasted for three hours at home. She was taken to hospital because of syncope. On admission to the coronary care unit the systolic blood pressure was 80 mmHg and the heart rate was 75 per minute. All peripheral pulses were feeble. In the aortic region a 2/6 ejection systolic murmur was heard. There was evidence of right ventricular failure and the central venous pressure was 21 cm H_2O. The electrocardiogram showed sinus rhythm at 75 per minute and it was unremarkable except for a diffusely abnormal repolarisation, with a straight ST segment and flat T wave, mainly in the lateral and inferior wall. The chest *x*-ray film showed a moderate cardiomegaly and a prominent dilatation of the ascending aorta. Under fluoroscopy the cardiac silhouette was hypokinetic. The echocardiogram disclosed an external diameter of the aorta of 72 mm; in the anterior wall two well-defined and parallel echoes, separated by a distance of 22 mm, were recorded; and in the posterior wall a similar double contour, 22 mm wide, was recorded. The echoes of the aortic leaflets showed a poor systolic opening followed by an early closure motion and reopening with slight fluttering. The left atrium measured 10 mm at this level (Fig. 1). Pericardial effusion was present.

Aortography confirmed the diagnosis of dissecting aneurysm and excluded the presence of aortic regurgitation. The patient was immediately transferred to theatre but died on her way to the operating room.

Necropsy

There was a dissecting aneurysm of the ascending aorta which ruptured into the pericardium and the pleura (haemothorax of 3000 ml). The histological examination showed cystic medial necrosis and moderate atheromatosis.

CASE 2

A 49-year-old white man, with a known history of arterial hypertension of 20 years' duration, was admitted to the coronary care unit because of oppressive retrosternal pain radiating to the epigastrium accompanied by heavy sweating. On admission, the blood pressure was 180/80 mmHg and the heart rate 70 per minute. The carotid pulse was brisk and wide, and the rest of arterial pulses were normal. In the aortic area, a 2/6 ejection systolic murmur and a 2/6 decrescendo high pitched diastolic murmur were heard. The electrocardiogram showed sinus rhythm at 70 beats per minute and there was evidence of left ventricular hypertrophy. The *x*-ray film of the thorax showed a

Received for publication 30 July 1979

dilated ascending aorta. The echocardiogram showed absence of fluid in the pericardium. The external diameter of the aorta was 47 mm at the aortic mitral transition level, increasing progressively up to 56 mm when the transducer was directed slightly upwards and inwards. In the posterior wall, two parallel echoes separated by a width of 14 mm were recorded. The anterior aortic leaflet, following a normal systolic opening, showed an early backwards motion, remaining in an intermediate position during the rest of the systole (Fig. 2). The anterior mitral leaflet showed slight diastolic fluttering.

The patient was treated with nitroprusside and propranolol and aortography was performed the day after his admission. A false lumen starting at the aortic root level and continuing towards the descending aorta was found. The aortic regurgitation was moderately severe. The patient was operated upon and a prosthetic aortic valve and Dacron aortic graft were implanted. The patient died suddenly 30 minutes after operation.

Discussion

The echocardiographic diagnosis of aortic root dissection is based on the criteria reported by Nanda *et al.*[2]: (1) enlargement of the external diameter of the aortic root (42 mm or more); (2) widening of the anterior and posterior aortic wall above 16 and

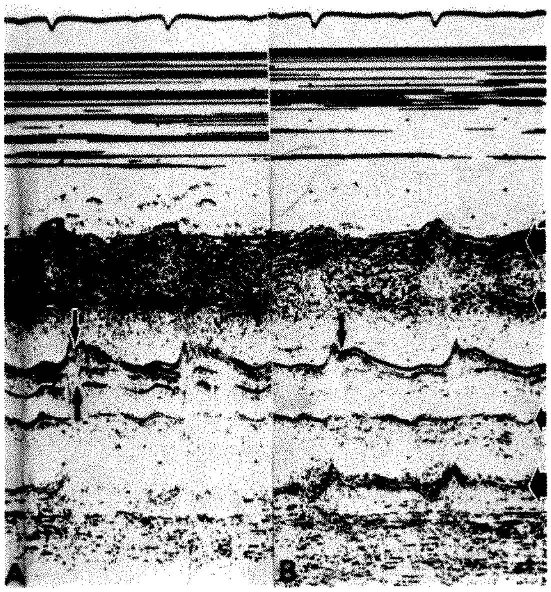

Fig. 1 *Case 1.* (A) *Valvar aortic echoes separate at the beginning of systole and join again immediately afterwards* (vertical arrows); *they are followed by a slight reopening during the rest of systole with a slight fluttering.* (B) *The echoes of the intima are recorded* (small horizontal arrows) *at 22 mm from the external layer of the aorta* (large horizontal arrows) *anteriorly and posteriorly.*

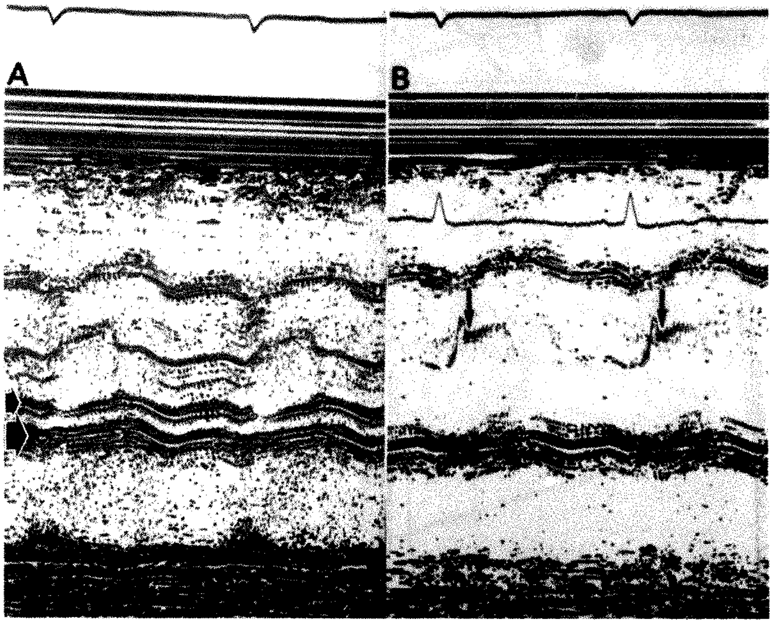

Fig. 2 *Case 2. The characteristics of the aortic root and the leaflets vary according to the transducer orientation.* (A) *The external diameter of the aorta is 47 mm and a double contour* (horizontal arrows)*, separated by 14 mm from the posterior wall, is seen.* (B) *The external diameter of the aorta is 53 mm, and opening of the anterior aortic leaflet followed by an early systolic partial closure* (vertical arrows) *and slight fluttering during the* *f systole are shown.*

10 mm, respectively; (3) maintenance of parallelism between the separated margins of the walls with normal aortic leaflets; (4) 8 mm or more variation in the width of the aortic wall, with only small changes in the direction of the transducer. For a definite diagnosis of dissecting aneurysm of the aorta several other conditions have to be considered. Aortic dilatation,[2 4 5] aortic calcification,[6] and pericardial effusion in the transverse sinus[2] have to be ruled out. On other occasions, echoes of the tricuspid ring, ventricular septum, right atrial appendage or pulmonary artery[7] can be mistaken for a dissection of the anterior aortic wall. Likewise, false negative echocardiographic recordings of a dissecting aneurysm involving the lateral wall of the ascending aorta are possible, since this wall is not reached by the ultrasonic beam.

Our two patients showed an early systolic closure of the aortic valve in addition to the typical echocardiographic signs of dissecting aneurysm of the aorta. The early systolic closure of the aortic leaflets was described by Davis *et al.*[8] as a pertinent finding of discrete subaortic stenosis, though later it was also seen in some cases of mitral regurgitation and intraventricular septal defect.[9] Felner and Schlant,[10] in a case of aortic root dissection, interpreted as a flap of the intima an echocardiographic finding very similar to the one found in our patients. Kasper *et al.*,[11] with a suprasternal echocardiographic recording, also found this sort of motion of the intima in another case of aortic root dissection. Nevertheless, in our echocardiographic recordings it is clear that the movement of early systolic closure is produced by the aortic leaflets and not by the intima, which was clearly recorded separately from them. This early systolic closure of the aortic leaflets could be related to the special haemodynamic conditions created by dissection of the proximal aorta during the first phase of systole: the initial bolus of the blood-stream produced by ventricular contraction would open the leaflets, but the areas of low pressure around this initial jet in a dilated aorta would produce a distortion of the stream prompting an early systolic valvar closure. Though we certainly feel that this is not a pathognomonic sign of this entity we do think it is important to keep it in mind as a complementary finding in the differential diagnosis of aortic root dissection.

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Br Heart J 1980; **43:** 582–88

Exercise-induced ST segment elevation

Electrocardiographic, angiographic, and scintigraphic evaluation

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SUMMARY Two hundred and fifteen patients with previous myocardial infarction were investigated between four and six months after the acute episode by computer assisted 12 lead exercise electrocardiography. Thirty-six (17%) out of this group showed ST segment elevation over the infarct zone, reflected by leads presenting with "QS" configuration. They were further investigated by serial thallium-201 scintigraphy, coronary arteriography, and left ventricular angiography. All showed left ventricular wall motion abnormalities and 89 per cent were diagnosed to have left ventricular "aneurysm" (dyskinesia and akinesia). In a further patient with a posterior aneurysm, the exercise-induced ST elevation could only be detected by using an oesophageal lead.

We suggest that these changes reflect severe underlying left ventricular wall motion abnormalities in the presence or absence of reversible myocardial ischaemia. The mechanism of ST segment elevation in this situation, occurring in leads with a "QS" configuration, may be mechanical in the majority of the patients rather than due to reversible myocardial ischaemia.

ST segment depression induced by exercise is recognised as the prime criterion for ischaemia but ST segment elevation during exercise is rarely seen and its exact mechanism and clinical significance are not clearly understood. Exercise-induced ST segment elevation has been reported as indicative of severe myocardial ischaemia,[1–5] and of abnormal left ventricular wall motion.[6–11] We investigated 37 patients who showed such changes with the object of elucidating the mechanisms and defining the clinical significance of exercise-induced ST segment elevation.

Patients and methods

Of a total of 215 patients with previous transmural infarction undergoing routine assessment (188 anterior, 26 inferior, and one true posterior), 36 patients showed ST segment elevation in one or more leads of the 12 lead electrocardiogram on exercise. The patient with the true posterior infarction showed ST elevation only in an oesophageal lead.

EXERCISE TESTING

Treadmill exercise testing was performed with a modified Balke's procedure (Table 1) using a computer-assisted system (CASE, Marquette Electronics) four to six months after the acute episode. A standard 12 lead electrocardiogram was recorded in the supine and standing postures before exercise, every minute during exercise, and in the post-exercise period. Three unipolar chest leads with

Table 1 *Modified Balke's treadmill exercise procedure*

Stage	*Time (min)*	*Speed (mph)*	*Gradient (%)*
I	3	2	0
II	3	3	4
III	3	3	8
IV	3	3	12
V	3	3	16
VI	3	3	20
VII	3	4·5	20
VIII	3	6	20

* Supported by the British Heart Foundation.

Received for publication 31 December 1979

maximum "Q" wave depth were continuously monitored by an on-line digital computer during exercise. A symptom-related maximal exercise end-point was used unless exercise had to be terminated because of dangerous arrhythmias. Systolic blood pressure was measured every three minutes during exercise using a standard mercury sphygmomanometer.

Significant ST segment deviations were defined as 1 mm of ST segment depression or elevation from the baseline occurring either during exercise or recovery or both.

To standardise the degree of ST segment elevation between patients the displacement of the ST segment was measured in each lead with a "QS" configuration and a mean ST segment displacement per lead was calculated at rest and at the maximal change during exercise. A mean ST segment at rest (STR) and a mean maximal exercise-induced ST segment elevation (STE) were calculated.

Concomitant ST segment depression was similarly measured from the 12 lead electrocardiogram.

ANGIOGRAPHY

Selective coronary and left ventricular cine-angiography was performed in multiple views using the Judkins technique[12] in all patients. Significant coronary artery narrowing was defined as 70 per cent or more luminal narrowing of major vessels and 50 per cent or more luminal narrowing of the left main stem coronary artery (LMS). Left ventricular angiograms were classified as normal, dyskinetic, akinetic, and hypokinetic with or without asynergy.[13]

THALLIUM-201 MYOCARDIAL IMAGING

A scalp-vein needle was placed in a forearm vein and flushed with heparinised saline to facilitate the rapid injection of thallium-201 during exercise. The patient was exercised till the previously determined maximal end point limit was reached, 1·5 mCi of thallium-201 was injected, and exercise was continued for at least another 15 seconds. Electrocardiographic monitoring was carried out throughout the exercise and until ST segment changes reverted to pre-exercise baseline. Before each series of studies a phantom that gave an image similar to a heart was recorded on 70 mm film (Kodak PF) using a high resolution, low energy parallel hole collimator (Searle Radiographic Pho/Gamma 111 HP). The 20 per cent window was centred on the 75 keV peak and 200 000 counts were collected at a series of intensity settings on the cathode ray tube. The image with the highest contrast was selected and the entire series of studies was carried out using that intensity setting.

Scintigrams were taken immediately after exercise, and approximately one-and-a-half hours and five hours after exercise. Anterior, 45° left anterior oblique, and left lateral views were obtained on each occasion.

A closed circuit television system was used to give an enlarged view of the exercise images with background subtraction and contrast enhancement preset using the television monitor controls, and this setting was constant for reading all the scintigraphic data in identical fashion.

A focal defect present at rest was interpreted as suggesting a previous myocardial infarction "scar". If the focal defect increased or appeared with the stress scintigram this was interpreted as indicative of myocardial ischaemia and was termed a "positive" scintigram.

Two observers independently interpreted and reported the scintigrams and angiograms with no knowledge as to the patient's identity or clinical history.

Results

There were two women and 35 men in the study with ages ranging from 34 to 67 years. Thirty-two had anterior myocardial infarction, four had had inferior myocardial infarction, and one had a true posterior infarction. The latter has been considered separately from the main group of 36 in the analysis because the exercise-induced ST elevation could only be detected by using an oesophageal lead. The time of investigation was at an interval of four to six months after infarction (mean 5·3 months).

EXERCISE DATA

Only 56 per cent of patients had elevated ST segments on the resting electrocardiogram. The mean resting ST level (STR) was 0·4 ±0·1 mm SE. The mean ST segment level on peak exercise (STE) was 2·9 ±0·2 mm SE. The mean resting heart rate was 79 ±2 SE beats/min and the mean maximum heart rate achieved during exercise was 135 ±3 SE beats/min. The mean resting systolic blood pressure was 127 ±2 SE mmHg and the mean of the peak exercise systolic blood pressure was 135 ±4 SE mmHg. Seventeen had a normal blood pressure response to exercise. Those with a fall in blood pressure (nine patients) or no change in systolic blood pressure on exercise (10 patients) were described as having an "abnormal" blood pressure response. Exercise-limiting symptoms were dyspnoea in 17, fatigue in eight, and chest pain in seven. In four the exercise was stopped because of significant arrhythmias. Ventricular ectopic beats were present in six at rest, but 16 developed ventricular arrhythmias on exercise and one patient had a run of ventricular tachycardia which spontaneously reverted to sinus rhythm.

ANGIOGRAPHIC DATA

All 36 patients had abnormalities of left ventricular wall movement; 32 had either dyskinesia or akinesia or a combination, and were, therefore, identified as having an "aneurysm"[13]; four had either hypokinesia or asynergy or both and the appearance was not diagnostic of an aneurysm. Insignificant mitral regurgitation was present in four patients.

Coronary arteriography revealed single vessel disease in 16 (45%) (15 anterior, one inferior myocardial infarction (AMI, IMI)), two vessel disease in 12 (33%) (9 AMI, 3 IMI), and triple vessel disease in eight (22%) (all 8 AMI). Out of 32 patients with anterior myocardial infarction two had incomplete occlusion of the left anterior descending artery, and 28 (88%) had total occlusion of this artery. Of the four patients with inferior myocardial infarction, two had 70 per cent occlusion of the left anterior descending artery, one had 70 per cent occlusion of the circumflex artery (Cx), and all four had total obstruction of the right coronary artery (RCA). Significant disease of the left main stem was present in four (all had AMI). Out of 15 patients with anterior myocardial infarction and single vessel disease, 13 had total obstruction of the left anterior descending artery (LAD), and one had 90 per cent luminal narrowing of the left anterior descending artery.

THALLIUM-201 SCINTIGRAPHY

A resting myocardial perfusion abnormality was disclosed in all 36 patients studied. A "positive" exercise scintigram was reported in 13 patients. Only one out of 13 with a "positive" scintigram had single vessel disease and the rest had multiple vessel disease (Table 2).

Twenty-three (64%) had "negative" exercise scintigrams out of which 15 patients (14 AMI and one IMI) had single vessel obstruction, thus excluding the possibility of reversible myocardial ischaemia causing ST segment elevation (Fig. 1 and 2).

Out of 12 (11 AMI and one IMI) with multiple vessel disease and a "positive" scintigram, six showed no evidence of ST segment depression in reciprocal leads (Fig. 3 and 4).

A prominent right ventricular image on the scintigram was obtained in three patients immediately after exercise and all three had a resting pulmonary capillary wedge pressure in excess of 19 mmHg (omega-sign[14]) (Fig. 5).

Table 2 *Summary of angiographic, exercise, and scintigraphic charges in all 37 patients*

Case no.	*LV angiography*				*Coronary arteriography*				*Reciprocal ST depression exercise*	*'Positive' ^{201}Tl scintigraphy exercise*
	Dys	*Akin*	*Hypo*	*Asyn*	*LMS*	*LAD*	*Cx*	*RCA*		
1	+	–	–	+	–	t	–	–	–	–
2	+	–	+	–	–	t	–	–	–	–
3	+	–	–	–	–	90%	–	–	–	+
4	–	+	+	–	–	t	–	90%	+	–
5	–	+	+	–	–	t	70%	90%	+	+
6	–	–	–	–	–	t	–	–	+	–
7	–	–	–	+	–	t	–	–	+	–
8	–	–	+	–	–	t	70%	–	–	+
9	+	–	+	+	–	t	70%	90%	+	+
10	–	+	–	–	–	t	–	70%	–	–
11	–	+	+	–	–	t	–	–	+	–
12	+	–	–	–	–	t	–	–	–	–
13	+	–	–	–	–	t	–	–	+	–
14	+	–	+	–	50%	t	–	70%	–	+
15	–	–	+	–	–	t	–	90%	+	+
16	+	–	–	+	–	t	70%	70%	–	+
17	+	–	–	–	–	90%	–	t	+	–
18	+	–	+	–	–	t	–	–	–	–
19	–	+	–	+	–	t	70%	70%	–	–
20	+	–	–	–	–	t	–	90%	+	+
21	+	–	–	–	–	t	–	–	+	–
22	+	–	+	–	–	t	–	–	–	–
23	+	–	–	–	–	t	–	70%	–	–
24	–	–	+	+	50%	t	70%	t	+	+
25	–	+	+	–	–	t	–	90%	+	+
26	+	–	–	–	–	t	–	–	–	–
27	–	+	–	–	50%	t	–	70%	–	+
28	+	–	+	–	–	t	–	–	+	–
29	+	–	–	–	–	t	–	–	–	–
30	–	–	+	–	50%	t	–	–	–	–
31	–	+	+	–	–	t	–	–	+	–
32	–	+	+	+	–	t	70%	70%	–	+
33*	–	+	–	–	–	–	70%	t	–	–
34*	+	–	+	–	–	70%	–	t	+	+
35*	+	+	–	–	–	70%	–	t	–	–
36*	–	–	+	–	–	–	–	t	+	–
37†	+	–	–	–	–	–	+	–	+	–

Dys, dyskinesia; Akin, akinesia; Hypo, hypokinesia; Asyn, asynergy; LMS, left main stem coronary artery; LAD, left anterior descending coronary artery; Cx, left circumflex coronary artery; RCA, right coronary artery; t, total occlusion; +, present; –, negative; %, percentage occlusion of coronary artery; 1–32, anterior myocardial infarction; *, inferior myocardial infarction; †, true posterior myocardial infarction.

CASE REPORT

The patient who had a true posterior infarction had a posterior left ventricular aneurysm and the circumflex artery was totally occluded at its origin; the rest of the coronary tree appeared free of atheroma. An exercise test with an oesophageal lead showed significant ST segment elevation in the oesophageal lead and ST segment depression in V2–V4 praecordial leads (Fig. 6). This patient had no cardiac pain but stopped exercise because of dyspnoea. There was a significant reduction in systolic blood pressure during exercise. Scintigraphy showed a perfusion defect in the posterior wall (best seen in the left lateral view) and no evidence of myocardial ischaemia was noted after exercise.

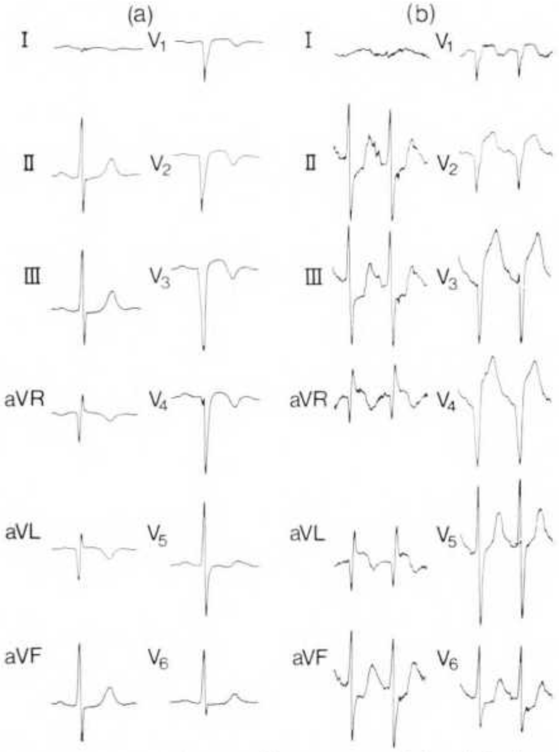

Fig. 1 *12 lead electrocardiogram at rest* (a) *and during maximal exercise* (b) *showing significant ST segment elevation over leads V2 to V4. Reciprocal ST segment depression is present in II, III, aVF, and V6.*

Discussion

Fortuin *et al.*[5] reported five cases with previous myocardial infarction and exercise-induced ST segment elevation occurring only in the leads with a "QS" complex. They ascribed this finding to myocardial ischaemia. Hegge *et al.*[4] and Atterhög *et al.*[1] suggested that exercise-induced ST segment elevation was the result of myocardial ischaemia without excluding left ventricular wall movement abnormalities. On the other hand, Chahine *et al.*[7] reported the presence of left ventricular aneurysm (86%) and previous anterior myocardial infarction and left anterior descending occlusion (85%) in patients with exercise-induced ST segment elevation.

Paine *et al.*[9] reported a "larger angiographic scar size" and lowered ejection fraction in 14 patients with ST segment elevation on exercise. Castellanet *et al.*,[8] Lahiri *et al.*,[11] Paine *et al.*,[9] and Weiner *et al.*[10] have produced evidence of a positive relation between left ventricular wall motion abnormalities and exercise-induced ST segment elevation.

Our study was designed to bring out the clinical significance of ST segment elevation in patients with ischaemic heart disease and to clarify the existing doubts as to its mechanism. The characteristic features were exercise-induced ST segment elevation associated with dyspnoea or fatigue (70%), abnormal or "poor" systolic blood pressure response to exercise, previous myocardial infarction, and abnormal left ventricular wall motion even at rest.

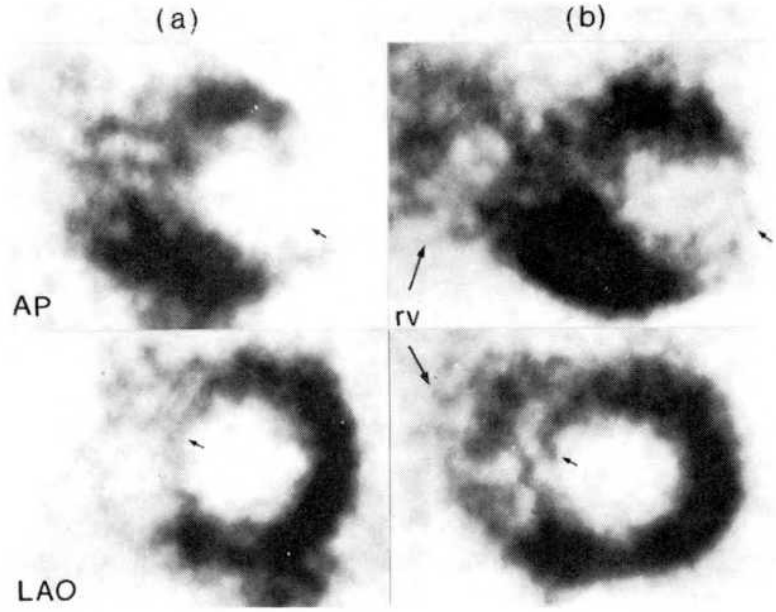

Fig. 2 ^{201}*Tl scintigrams of same patient as in Fig. 1, anteroposterior view (AP) and left anterior oblique (LAO) scintigraphic views at rest;* (a) *showing a large perfusion defect in the anterior (AP) and septal walls (LAO) representing the infarction "scar". There is no relative alteration of regional myocardial perfusion during exercise* (b). *rv, right ventricular image.*

We did not attempt exercise left ventriculograms as the resting films showed that 89 per cent of the patients had left ventricular "aneurysms". We considered that a powered injection into the ventricle during exercise could be dangerous when such significant left ventricular abnormality was already present at rest.

Thallium-201 scintigraphy was used as an indicator of myocardial ischaemia to determine whether ischaemia occurred during exercise-induced ST segment elevation. In 15 out of 16 patients with single vessel disease a "negative" ^{201}Tl scintigram was obtained during exercise-induced ST segment elevation, but an infarction "scar" was visualised at rest in all patients.

Even though it is difficult to exclude the absence of ischaemia in the infarction zone and its surrounding area, the development of reversible ischaemia as a cause of ST segment elevation in these areas in response to dynamic exercise was excluded by thallium-201 scintigraphy. However, exercise-induced reversible regional myocardial ischaemia was observed in 13 (36%). Reversible ischaemia was noted to occur in the zone surrounding the infarct "scar" (four cases), or in a different region from the site of infarction (nine cases).

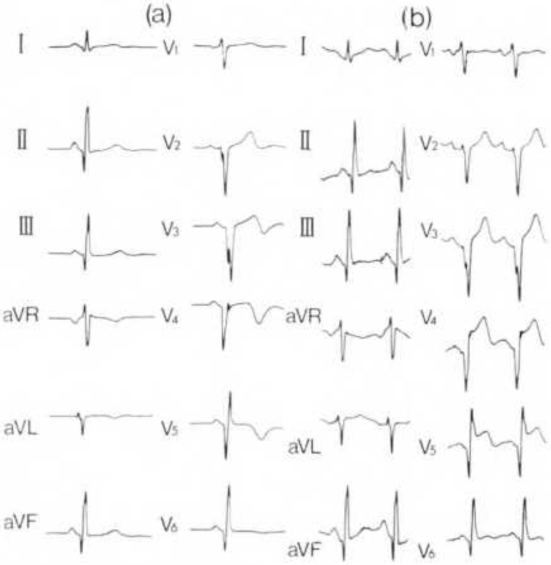

Fig. 3 *12 lead electrocardiogram at rest showing an anterolateral myocardial infarction* (a) *and significant ST segment elevation on exercise* (b) *in V3 to V5 but no ST segment depression is noted in this patient with triple vessel disease and "positive" scintigraphy.*

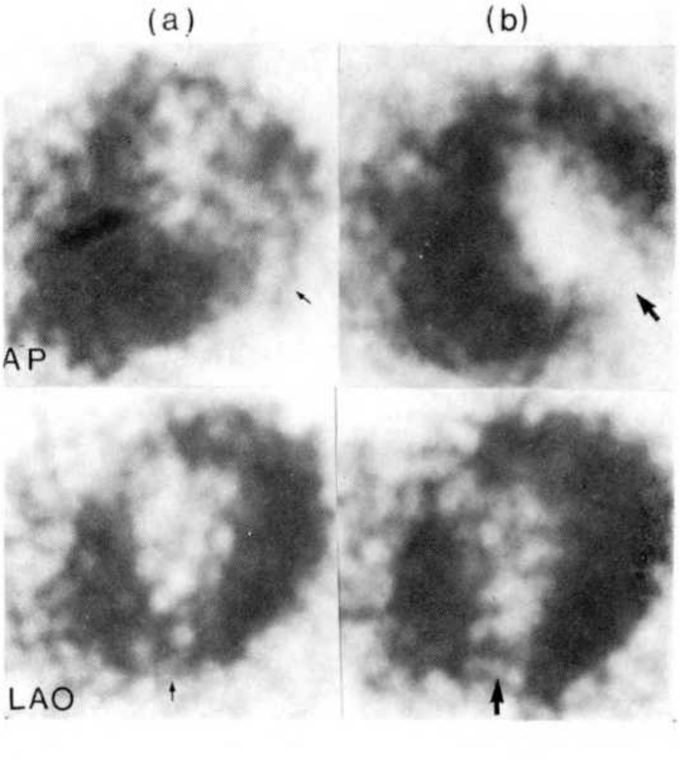

Fig. 4 *^{201}Tl myocardial scintigrams of the same patient as in Fig. 3, in the resting* (a) *anteroposterior (AP) and left anterior oblique (LAO) views showing perfusion changes in the anteroapical and inferior walls* (small arrows) *and a reduction of relative perfusion during exercise* (b) *in the apical and inferior walls* (large arrows) *in a patient with no exercise-induced ST segment depression.*

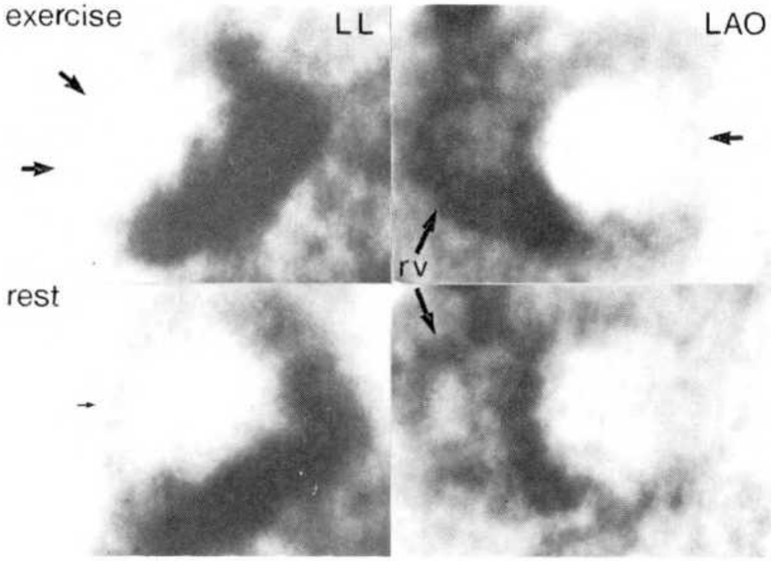

Fig. 5 ^{201}*Tl scintigram at rest and exercise in the left anterior oblique (LAO) and left lateral (LL) views showing exercise-induced ischaemia in the left lateral and left anterior oblique views and a prominent right ventricle ("omega sign") indicating severe left ventricular dysfunction during exercise.*

There is some controversy regarding the specificity and sensitivity of ^{201}Tl scintigraphy in detecting myocardial ischaemia when exercise images are compared with late redistribution images (five to six hours) as opposed to imaging performed at rest. However, the majority of authors feel that redistribution imaging is as sensitive as rest scintigraphy.[15–20] Two-thirds of these patients did not show any evidence of reversible perfusion abnormalities in the late redistribution images. However, in 12 patients with a "positive" redistribution image there was evidence of severe multiple vessel pathology.

The use of an oesophageal lead indicated exercise-induced ST segment elevation with ST segment depression in the praecordial leads (V1 to V4) in one patient. In this case a large area of dyskinesia on the posterior surface of the ventricle was detected and the anterior ST segment depression, which was associated with a "negative" exercise scan, was a reciprocal change from the ST segment elevation documented by the oesophageal lead. Castellanet *et al.*[8] have also suggested that inferoposterior ischaemia is indicated when exercise-induced ST segment elevation occurs specifically over the V1 praecordial lead. This rare finding

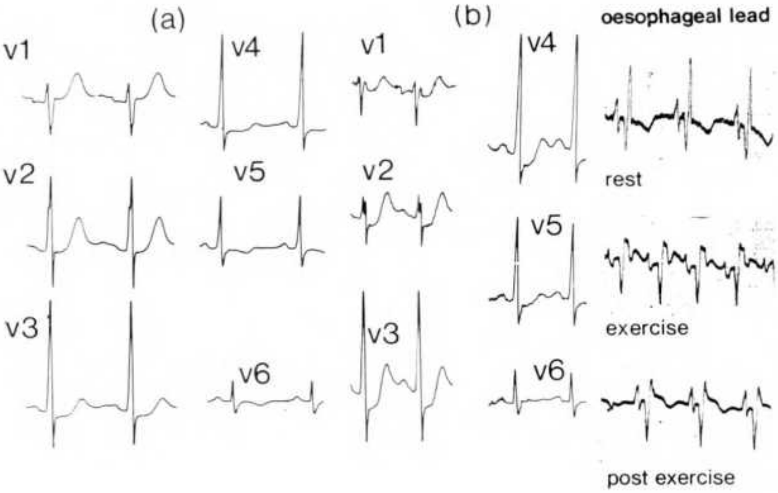

Fig. 6 *Praecordial electrocardiogram leads at rest* (a) *in the patient with a posterior aneurysm after myocardial infarction showing ST-T depression mainly in V3. During exercise* (b) *ST segment depression is noted in V1 to V5. Simultaneous oesophageal lead electrocardiogram at rest shows a "QS" pattern and "T" wave inversion, and significant ST segment elevation is noted during exercise and in the post-exercise periods.*

supports the contention that local wall motion abnormalities are responsible for ST segment elevation in this context.

In conclusion, we believe that exercise-induced ST segment elevation occuring during exercise in the leads presenting with a "QS" configuration (over the infarction "scar") of a 12 lead electrocardiogram is likely to be the result of abnormal left ventricular wall motion in the presence or absence of myocardial ischaemia.

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Br Heart J 1980; **43:** 589–92

Histopathological study on right endomyocardial biopsy of Kawasaki disease

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SUMMARY Fifty right ventricular endomyocardial biopsy specimens taken from patients withKawasaki disease were studied. These were taken from 33 male and 17 female patients.

Biopsies were examined for inflammatory cell infiltration, fibrosis, myocardial fibre disarrangement, and the cellular and nuclear changes of hypertrophy. A score of severity was prepared. The degree of abnormality was found to correlate with the duration of the disease, as did fibrosis found in 18 cases (36%), but inflammatory cell infiltration did not (13 cases, 26%).

Coronary involvement was restricted to the male patients but the myocardial changes occurred in both sexes.

In 1974, Kawasaki and his colleagues[1] reported a new disease which they had observed over some years. Children presented with fever, conjunctival congestion, pharyngitis, lipoedema, cervical lymphadenopathy, and a polymorphous exanthematous rash on the trunk. Though the disease was initially thought to be benign it became apparent that a proportion of patients died suddenly. Detailed morphological studies of the heart at necropsy were widely reported.[2–6] Such studies showed death to be related to a generalised myocarditis which may include the atrioventricular conduction system and an intense coronary arteritis, the latter leading to ischaemic myocardial damage or actual coronary artery rupture with haemopericardium.

The disease remains of unknown aetiology and the prognosis is still unresolved. Death may be related as much to the myocarditic element as to the coronary arterial component.

This hypothesis is supported by the present paper. Fifty right ventricular endomyocardial biopsies taken from patients with Kawasaki disease were examined. All showed myocardial architectural disorganisation with hypertrophy on histological examination, and the findings suggest that such changes are progressive.

Subjects and methods

Right ventricular endomyocardial biopsies obtained at cardiac catheterisation from 50 patients with Kawasaki disease were collected and studied at the Department of Pathology, National Cardiovascular Center in 1978 and 1979.

In all patients, the clinical diagnosis was based upon agreement with the guidelines prepared by the Mucocutaneous Lymph Node Syndrome (MCLS) Research Committee of the Ministry of Health and Welfare of the Japanese Government in 1974.

In addition to physical and radiological examination, investigation included echocardiography and selective coronary angiography. The age and sex distribution at onset are shown in Fig. 1. Those patients with radiologically abnormal coronary arteries are indicated. All were male. Fig. 2 analyses the length of history.

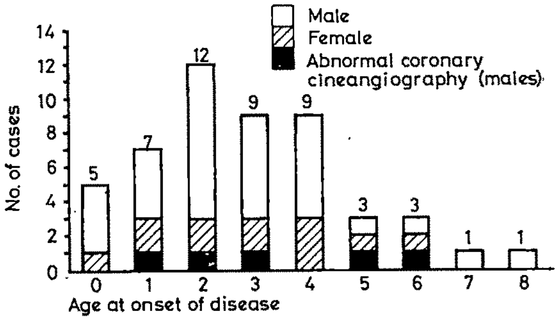

Fig. 1 *Age distribution at onset of Kawasaki disease.*

Received for publication 26 November 1979

Biopsy specimens were taken from the free wall of the right ventricle using Konno's biotome. One specimen was placed in buffered 10 per cent formalin for paraffin section, the other in 2·5 per cent glutaraldehyde for study by electron microscopy.

Tissue blocks were sectioned at a thickness of approximately 5 μ and stained with haematoxylin-eosin, periodic acid-Schiff, and trichrome.

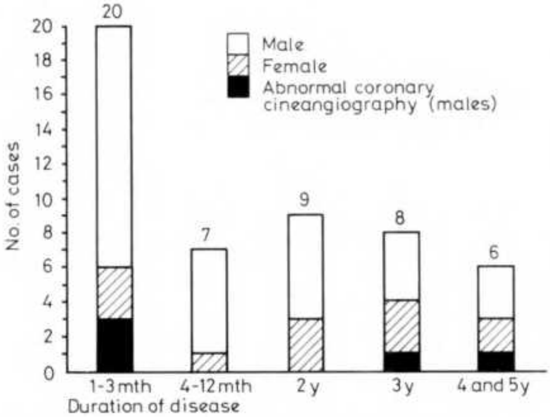

Fig. 2 *Duration of disease before endocardial biopsy.*

The histological criteria of myocardial morphology studied were those of Okada,[7] Sekiguchi and Konno,[8] and Van Noorden *et al.*[9] Each of these criteria was graded 0 to 3 according to severity and the total scores were plotted. Each individual component of the score represented the total scores of three independent observations. Typical findings are illustrated in Fig. 3. The presence of inflammatory changes and of fibrosis were also noted.

Lastly, five biopsies taken from other subjects, which were collected to show normal myocardium, were also subjected to the scoring procedure for abnormal myocardial morphology. These were used as controls.

Results

(1) INFLAMMATORY LESIONS (Fig. 4)

Inflammatory cell infiltration was found in 13 cases (26%). It was slight and consisted of small lymphocytes and occasional plasma cells. No acute or active inflammatory changes were seen. The presence of these infiltrates seemed to be unrelated to the duration of the disease.

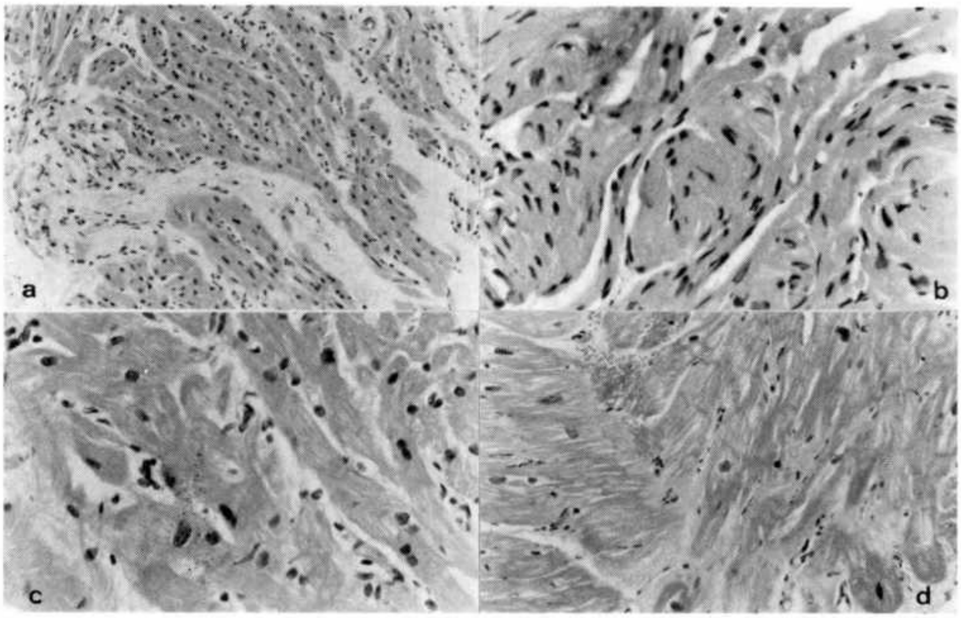

Fig. 3 *Typical biopsy findings:* (a) *obvious disarray of myocardial fibres with nuclear proliferation, swelling, and duplication (H and E, original magnification ×100);* (b) *myocardial whorling (H and E, original magnification × 100);* (c) *varying size of the myocardial fibres and nuclei, with abnormal branching (H and E, original magnification ×400);* (d) *myocardial hypertrophy with disarray and fibrosis (H and E, original magnification ×400).*

(2) FIBROSIS (Fig. 5)
Eighteen cases (36%) showed fibrosis of varying degree and the incidence seemed to be related to the duration of the disease.

(3) TOTAL SCORES OF HISTOLOGICAL FINDINGS
Individual scores are plotted against duration of the disease in Fig. 6.

The coefficient of correlation is only 0·59 ($p < 0.05$). The five cases with abnormal coronary cineangiograms are included in Fig. 6. Fig. 7 shows an example from a case biopsied five years after the onset of the disease.

Discussion

In Kawasaki disease, in addition to necrotising coronary arteritis with thrombosis, there is also myocarditis.[3 6]

This extends into the interstitial tissue and results in myocardial oedema, and degeneration; it has been elegantly demonstrated by immunofluorescence techniques which have shown diffuse deposits of myocardial intracellular IgG.[3]

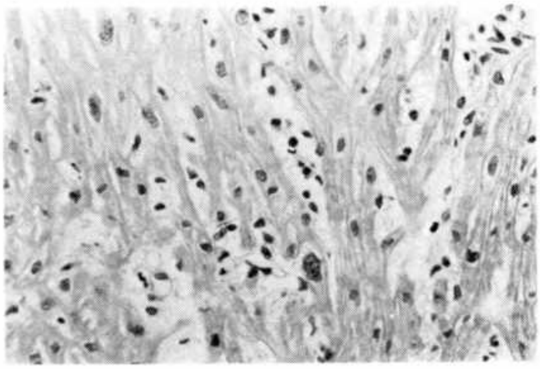

Fig. 4 *Inflammatory small cell infiltration in the interstitial tissue and lace-like changes in the myocardial fibres (H and E, original magnification × 200).*

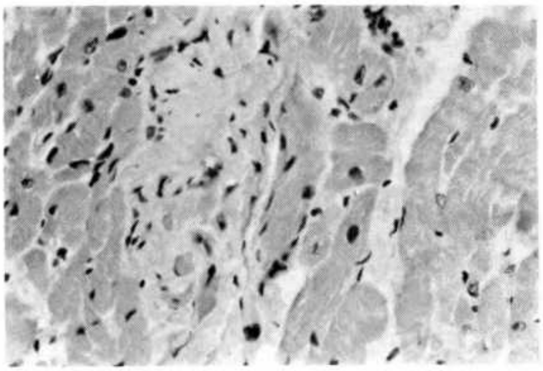

Fig. 5 *Focal fibrosis involving several myocardial fibres (H and E, original magnification, × 200).*

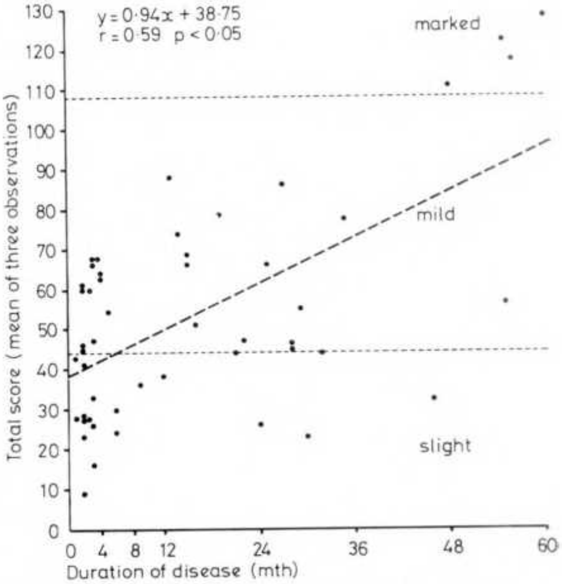

Fig. 6 *Correlation of abnormal myocardial morphology score and duration of the disease.*

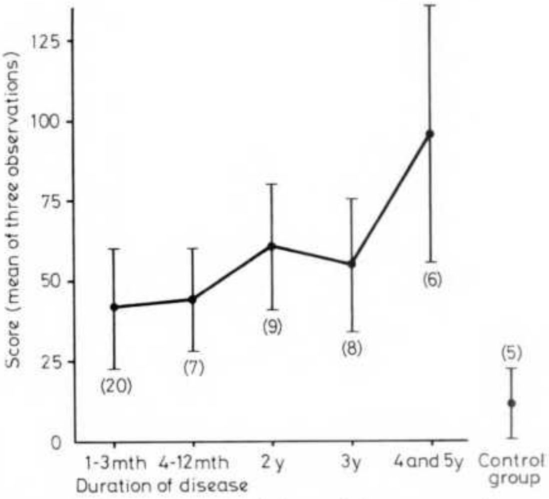

Fig. 7 *Abnormal myocardial morphology score and duration of disease.*

Tanaka *et al.*[2] consider it to be a pancarditis. Most cases coming to necropsy we found to have died from ischaemia caused by the necrotising arteritis, which is thought to be similar to that found in infantile periarteritis nodosa.[2 5] Myocarditis receives little mention but it is possible its persistence is the cause of part, at least, of the myocardial changes which occur in the course of the disease. In our study, chronic interstitial myocarditis did not correlate with the duration of the disease. Interstitial fibrosis which can be distinguished from ischaemic myocardial fibrosis was related to duration and may follow the myocarditis. Perhaps the primary pathology in Kawasaki disease is an inflammatory process which can affect either the coronary arteries or the myocardium and interstitial tissue.

Our review of the myocardial changes also included assessment of myocardial fibre hypertrophy or arrangement. Myocardial hypertrophy and disarray also correlate with duration and it was clear that the overall myocardial abnormality was related to duration.

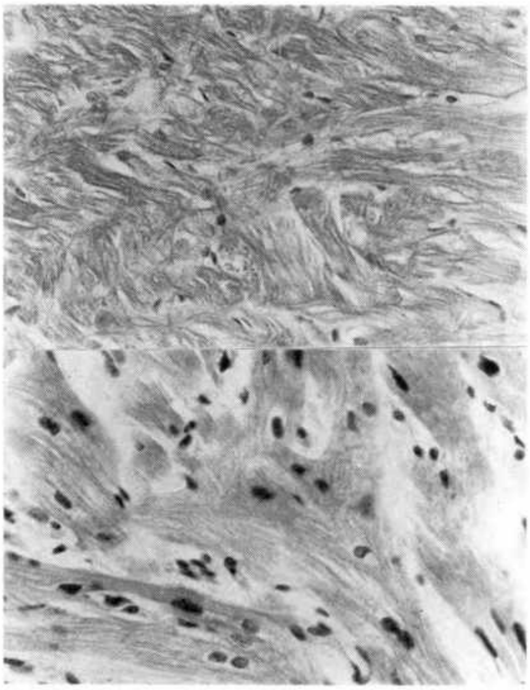

Fig. 8 *Severe histological changes in a case of five years' standing (H and E, original magnification × 400).*

In long-standing cases, some biopsies showed such abnormality of arrangement including whorling that HOCM was simulated histologically. The mechanism of protection of such changes is poorly understood at present. Abelmann,[10] among others, has shown similar disarray after viral myocarditis.

Kawasaki disease occurs more often in men than in women, but though the involvement of the coronary arteries was restricted to the male patients, the myocardial changes were present in both sexes.

If the disease is caused by infection, the aetiological agent, whether viral, rickettsial, bacterial, or fungal, remains to be discovered, and the importance of this relative to the coronary arteries, particularly of small vessels beyond the reach of coronary angiography, remains unresolved.

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Br Heart J 1980; **43:** 593–6

Right ventricular outflow tract obstruction secondary to small intestinal lymphoma

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SUMMARY A 71-year-old man developed symptoms and signs of right ventricular outflow obstruction. After angiography, which showed multiple lobulated and well-defined filling defects in the right ventricular outflow tract, endomyocardial biopsy disclosed infiltration of the myocardium by a poorly differentiated malignant neoplasm. At necropsy he was found to have a small intestinal lymphoma.

Case report

A 71-year-old man was admitted with a seven-month history of progressive exertional dyspnoea, extreme tiredness, anorexia, and sweats. There was no relevant past history and he had been on no medication.

On examination, he was pale but not clubbed and he had no lymphadenopathy. The heart rate was normal and the blood pressure 140/80 mmHg. The central venous pressure was raised 10 cm above the sternal angle, with a prominent a wave, and the apex beat was displaced to the anterior axillary line in the sixth intercostal space. Auscultation showed an early diastolic sound which was either a delayed pulmonary component of the second sound or a right ventricular third sound. There was a grade 4/6 ejection systolic murmur maximal at the pulmonary area. There was a trace of ankle oedema and the liver was palpable 3 cm below the costal margin and was of normal consistency and not tender. The spleen was impalpable and examination was otherwise unremarkable.

INVESTIGATIONS

The haemoglobin was 10·9 g/dl with MCV 76 fl. and a mildly hypochromic film. The white count was 8500/mm^3 with a norma]differential and the erythrocyte sedimentation rate was 73 mm in one hour. The alkaline phosphatase and alanine transaminase were both marginally raised, but routine biochemical screen was otherwise normal, apart from a low iron and iron binding capacity. Protein electrophoresis showed an increased α-2 globulin. Sputum culture and cytology were negative. Bone-marrow aspiration showed reticuloendothelial iron block with anaemia, probably secondary to malignancy or infection.

The chest *x*-ray film (Fig. 1a) showed an enlarged heart with a prominent bulge on the upper left heart border. There was pleural shadowing at the left base and bullae in both lung fields. Mediastinal tomography showed a soft tissue shadow in the region of the right ventricular outflow tract, with a convex outer border. It was not possible to say whether this represented an intrinsic lesion of the heart itself or a mass outside the heart. Bronchoscopy was normal. The electrocardiogram showed left axis deviation and non-specific ST changes in the lateral chest leads. There was no evidence of right ventricular hypertrophy or right bundle-branch block.

The routine echocardiogram showed normal left ventricular cavity size, but the ventricular wall was hypokinetic. The interventricular septum was disproportionately thickened, and there were prominent echoes from the anterior heart wall, but with normal right ventricular cavity size. Using simultaneous high-speed echocardiography and phonocardiography, the early diastolic sound noted on auscultation was shown to coincide with pulmonary valve closure, which was thus shown as being 0·08 seconds after aortic closure in expiration. These findings were consistent with right ventricular outflow tract obstruction, but even in retrospect there was no evidence from the echocardiogram of a space-occupying lesion.

Cardiac catheterisation showed a gradient of

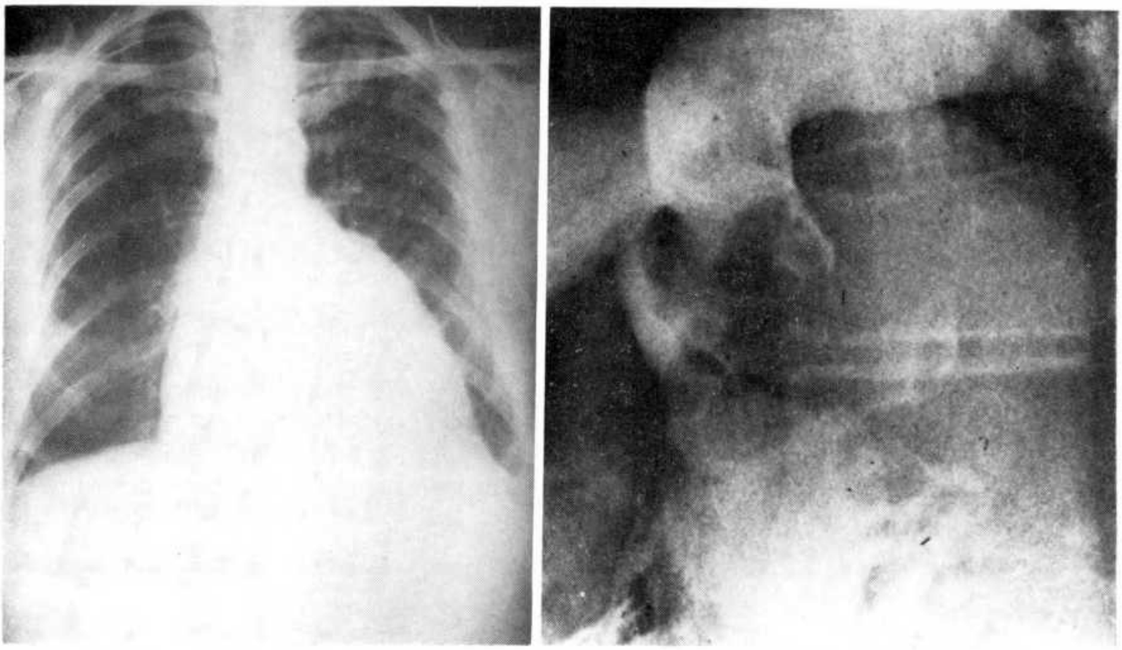


Fig. 1 (a) *Chest x-ray film showing an enlarged heart with a prominent bulge on the upper left heart border.* (b) *Right ventricular angiogram (oblique view), showing multiple lobulated filling defects in the outflow tract.*

55 mmHg across the right ventricular outflow tract, and angiography (Fig. 1b) showed multiple lobulated and well-defined filling defects in the right ventricular outflow tract which prolapsed into the main pulmonary artery during ventricular ejection.

SUBSEQUENT COURSE

The patient's condition steadily worsened after his admission, and he developed atrial arrhythmias. Surgical resection of the tumour was considered, and he thus underwent endomyocardial biopsy, using the technique described by Brooksby *et al.*[1] Though this procedure did not appear directly to affect the patient adversely, he continued to deteriorate over the subsequent week, becoming hypotensive with further arrhythmias, and died.

PATHOLOGY

The cardiac biopsy comprised five fragments of tissue. These showed infiltration of the myocardium by a poorly differentiated malignant neoplasm (Fig. 2a), the appearances of which were consistent with a malignant lymphoma or a poorly differentiated secondary carcinoma.

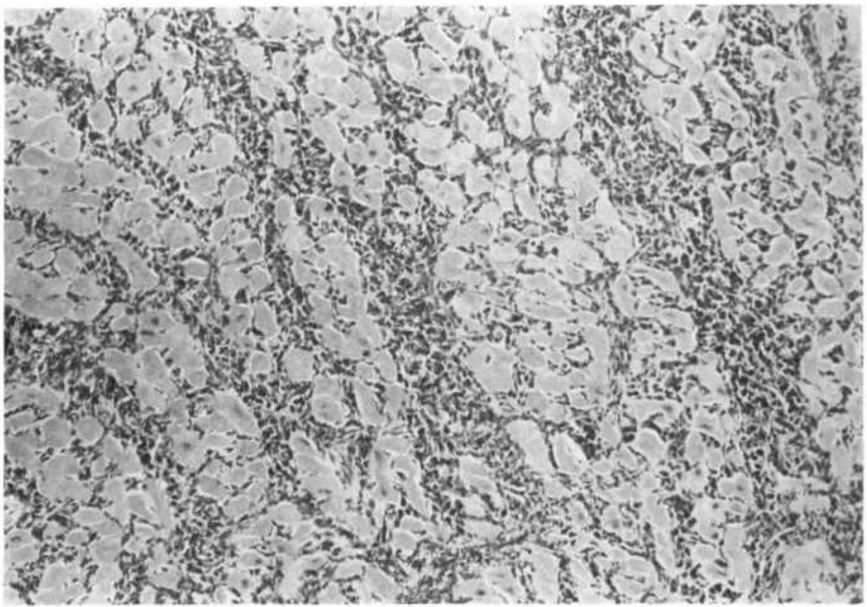
At necropsy, tumour was found infiltrating the right ventricular outflow tract, extending from 3 cm below the pulmonary valve to the bifurcation of the pulmonary artery (Fig. 2b). Only one cusp of the pulmonary valve was spared. Tumour was seen in the wall of the left atrium and in the anterior part of the wall of the left ventricle, but it did not encroach into either chamber.

Tumour was also seen in hilar and mesenteric lymph nodes, and in the small bowel. The multifocal nature of the tumour deposits in the small bowel mucosa is characteristic of a malignant lymphoma. Furthermore, such an appearance is highly suggestive of local origin of the lymphoma in the bowel, so that the cardiac deposits must be regarded as metastases. The liver was congested but contained no secondary deposits.

The histological appearances confirmed a malignant lymphoma of the poorly differentiated lymphocytic type.

Discussion

After several necropsy series the incidence of cardiac metastasis in patients with lymphoma is now known to be much higher than was previously thought. An incidence of 24 per cent was found[2] in 196 patients with a malignant lymphoma studied at necropsy, though the incidence of symptoms caused by cardiac involvement is probably less than 10 per cent of those with metastases. The



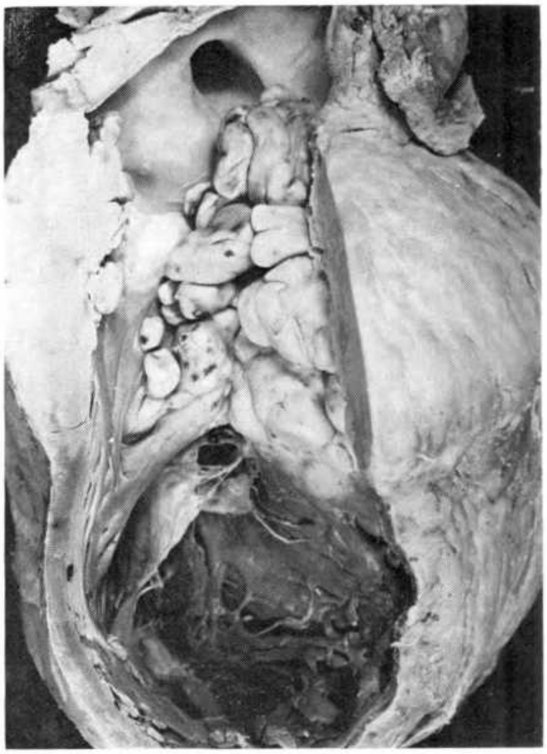
(2a)

Fig. 2 (a) *Cardiac biopsy; myocardial fibres infiltrated by a poorly differentiated malignant neoplasm.* (*Haematoxylin and eosin.* ×200.) (b) *Lobulated white tumour masses fill the right ventricular outflow tract, and the surrounding myocardium is thickened with tumour.*

most common site of involvement is the pericardium, and endocardial lesions are rare. Thus the usual form of presentation is with pericardial effusion or arrhythmias, often atrial fibrillation. Cardiac obstruction and embolism, common symptoms of primary heart tumours, are less common with metastases which tend to be invasive without producing space-occupying lesions.[3]

It is also rare for the cardiac manifestation to be the presenting feature in lymphoma, and we have been unable to find a similar case of a deposit from an occult small intestinal lymphoma producing symptomatic right ventricular outflow obstruction. Such a presentation, as indicated above, is well recognised in primary heart tumours, both rhabdomyosarcomata[4 5] and myxomata.[6]

The diagnosis of cardiac tumours may be difficult because of their extremely variable manifestations, but it is important in view of the possibility of treatment. Echocardiography has been shown to be of great value in the diagnosis, particularly of atrial myxomata, but also of right ventricular tumours,[7] though it should be noted that the echocardiograms reported by Ports *et al.* were initially interpreted wrongly, and only retrospectively was it shown that a correct diagnosis could have been made. In our case, combined echophonocardiography suggested that there was right ventricular outflow obstruction, but there



(2b)

were no abnormal echoes from within the right ventricular cavity to suggest a tumour.

Here the technique of endomyocardial biopsy was valuable. Firstly, it indicated that the tumour was invading the myocardium and was thus not amenable to a surgical approach. This is, fortunately, not the case if a myxoma is found, and Snyder *et al.*,[8] reviewing the published reports, stated that 11 out of 13 patients with right ventricular myxoma survived operation and no recurrence was noted, whereas other tumours had a poor prognosis. Secondly, the biopsy suggested lymphoma. The results of several studies clearly indicate the value of radiotherapy in cardiac lymphoma, both in terms of symptomatic improvement and, to some extent, prolonged survival. Radiotherapy can reverse arrhythmias and control pericardial effusions. Cham *et al.*[9] reported improvement in six out of seven patients for between two and four months; Terry and Kligerman[10] described seven patients of whom one was alive without evidence of the disease at two years, and another at one year. Radiotherapy was also used successfully by Liedtke *et al.*[11] in a case with secondary lymphoma obstructing the pulmonary valve and proximal pulmonary artery, with the patient continuing to improve over an eight-month follow-up period. Unfortunately, our patient's general condition was extremely poor, and he died before we could consider radiotherapy.

Despite the rarity of this case, it illustrates the need for a definitive diagnosis of cardiac tumour to be made, and the value of endomyocardial biopsy in establishing both the diagnosis and the possibilities of curative and palliative treatment.

We are grateful to Dr A Leatham and Dr D Redwood for allowing us to publish the details of this case.

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Br Heart J 1980; **43:** 597–9

Herpes zoster pericarditis

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SUMMARY A healthy 22-year-old man developed acute varicella pericarditis, characterised by an enanthem with diagnostic rising titres of varicella zoster antibodies but without the typical exanthem. This, the third reported case of varicella pericarditis, is the first to be documented without a typical varicella eruption.

Pericarditis and myocarditis are well-known complications of viral infections. These include Coxsackie B viruses, Coxsackie A viruses, Echoviruses, notably types 3, 6, and 19, influenza virus, Epstein-Barr virus, and polio virus (Bennett and Forbes, 1967; Bell and Grist, 1970; Grist, 1972; Haynes *et al.*, 1972; Shapiro *et al.*, 1973; Sainani *et al.*, 1975). Pericarditis may follow smallpox vaccination (Bengtsson *et al.*, 1966; Matthews and Griffiths, 1974). Though varicella myocarditis has been reported (Hackel, 1953; Moore *et al.*, 1969; Morales *et al.*, 1971), only 2 cases of varicella pericarditis have been reported (Mandelbaum and Terk, 1959; Helmly *et al.*, 1963). In both cases the pericarditis followed a typical varicella exanthem; this case is unique in that the typical rash was absent and the cardiac manifestations dominated the clinical picture.

Case report

A 22-year-old man, previously healthy, woke with discomfort in the upper chest, which, within a few hours, developed into severe central chest pain with dyspnoea and paraesthesiae in his fingers. On admission he was distressed, pale, and sweating, with a fever of 38·3°C. No other abnormality was noted; the heart sounds were normal and there was no pericardial friction rub.

Routine biochemical and haematological investigation was normal except for a white blood cell count of $14{\cdot}9\times10^9$/l. Chest *x*-ray film was normal but the electrocardiogram showed prominent elevation of the ST segments in leads II, III, aVF, V5 and 6 (Fig.). An initial diagnosis of inferolateral myocardial infarction was made. On the second day his temperature rose to 40°C and he developed severe painful ulcers in the left mandibular buccal sulcus associated with enlarged and tender cervical lymph glands. The white blood cell count was $11{\cdot}9\times10^9$/l (61% polymorphs and 35% lymphocytes). A pericardial friction rub was heard on the third day and his temperature became normal on the fifth day. Serum aspartate transaminase rose to 62 IU/l and the hydroxybutyric-dehydrogenase to 176 IU/l on the second day (normal values in the laboratory being 40 and 150 IU/l, respectively). The ST segment elevation of the electrocardiogram resolved by the third day, with subsequent T wave inversion in the same leads (Fig.).

Clinical recovery was uneventful. Virus serology showed a fivefold rise in herpes zoster complement-fixing antibodies from 4 to 128 and a similar, anamnestic, rise in herpes simplex antibodies (Table).

In view of the patient's youth, it was important to exclude coronary heart disease. As the electrocardiographic findings were compatible with either pericarditis or myocardial infarction, coronary arteriography was performed; this showed a normal coronary vascular tree without coronary artery disease and with normal left ventricular function. The electrocardiogram returned to normal after 5 months (Fig.), and the patient remains in good health 3 years later with no recurrence of pain, other cardiac symptoms, or electrocardiographic abnormalities.

Discussion

The association of varicella infection and myocarditis has been previously reported and has a high mortality probably because of systemic infection (Hackel, 1953; Moore *et al.*, 1969; Morales *et al.*, 1971). Varicella with pericarditis alone is rare. The only two previously reported patients (Mandelbaum and

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Table *Titres of viral complement-fixing antibodies*

	Days after onset of illness	
	1	*16*
Influenza A	4	<4
Influenza B	<4	<4
Adenovirus	8	<4
Psittacosis—*Lymphogranuloma vernereum*	<4	<4
R. burneti	<4	<4
Respiratory syncytial virus	8	8
N. pneumoniae	4	4
H. zoster	<4	128
H. simplex	<4	128
Coxsackie B	8	16

Terk, 1959; Helmly *et al.*, 1963) were young men. As both had typical varicella eruptions, the clinical diagnosis of varicella was straightforward. This case had an enanthem and a history of chest pain only. The electrocardiographic changes initially suggested myocardial infarction but the elimination of coronary disease and the raised antibody titres permitted correct diagnosis.

Although this patient lacked the characteristic cutaneous eruption of herpes zoster, the mouth ulcers noted in the early phase of the illness were probably a zoster eruption in the territory of the buccal nerve, a branch of the third division of the trigeminal nerve. The rise in complement-fixing antibodies was diagnostic of herpes zoster infection according to the criteria of Grist (1972), with an anamnestic rise in herpes simplex antibodies.

A review of findings in infants with varicella has suggested that electrocardiographic abnormalities may be more common than is usually suspected (Paci *et al.*, 1960). It is possible that pericardial or myocardial involvement in the absence of clinical symptoms may occur frequently and has been postulated in several viral illnesses (Ahlborg *et al.*, 1966; Lewes *et al.*, 1974). This case suggests that a rising titre of varicella antibodies in the viral serological screening of patients with acute benign pericarditis may increase the frequency with which varicella infection is diagnosed.

We thank Dr J M Hinton of St Richard's Hospital, Chichester, Dr Walter Somerville, and Brigader H S Moore for permission to publish details of this case.

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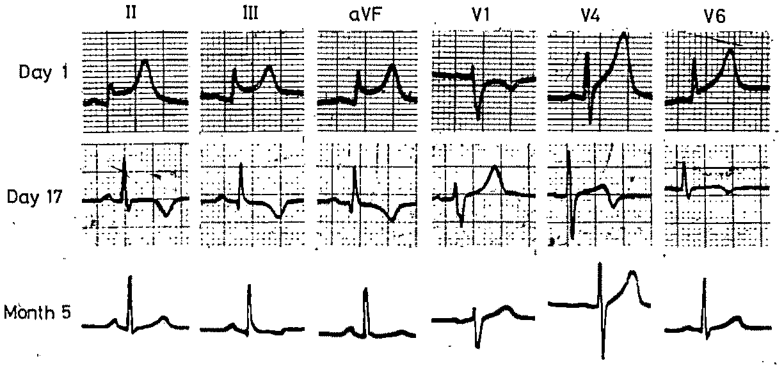
Fig. *Electrocardiographic changes showing ST segment elevation on day 1, maximum T wave inversion on day 17, and the return to normal after 5 months*



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Br Heart J 1980; **43:** 600–4

Evidence for a unidirectional retrograde communication between distal His bundle and atria*

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SUMMARY Intracardiac electrogram recordings are presented suggesting the existence in one patient with recurrent supraventricular tachycardia of a functionally unidirectional retrograde connection between the *distal* His bundle and the low right atrium. Recordings obtained during junctional rhythm showed a short ventriculoatrial conduction time which did not lengthen during rapid or premature ventricular pacing. During an episode of supraventricular tachycardia induced by a single atrial premature stimulus, an infra-His Wenckebach period occurred during which retrograde ventriculoatrial conduction remained constant until ventricular capture was blocked, but atrial activation persisted with the same retrograde atrial activation sequence seen in the previous beats of supraventricular tachycardia. The findings appear to document participation in supraventricular tachycardia of a type of atrio-His fibre originally described by Brechenmacher.

In 1974 and 1975 Brechenmacher presented histological evidence for the existence of atrial fibres bypassing the human atrioventricular node and terminating directly in the His bundle.[1 2] He found such direct atrio-His connections in only two of a series of 687 hearts studied histologically. He specifically differentiated the fibres from so-called 'James fibres', which pass from the atrium to the lower atrioventricular node or to the base of the tricuspid valve, and which both he and James consider to be present normally in most, if not all, human hearts.[2 3] The purpose of this paper is to present unusual electrophysiological findings in a single patient which are best explained by an atrio-His fibre of Brechenmacher functioning retrogradely only.

Case report

The patient was a 53-year-old woman who complained of a recurrent sensation of rapid heart action since adolescence which had recently worsened despite medical treatment. Twenty-four hours of ambulatory monitoring showed only two brief runs of supraventricular tachycardia with rates around 170 beats per minute. The resting surface electrocardiogram was within normal limits. The PR interval was 0·16 s and there was no delta wave. Electrophysiological study was undertaken to identify the mechanism of the arrhythmia and to identify an antiarrhythmic regimen which could prevent its recurrence.

Methods

The patient underwent intracardiac electrophysiological study. Quadripolar electrode catheters (interpolar distance = 1 cm) were advanced to the right atrium and the bundle of His position and a hexipolar electrode catheter was positioned at the right ventricular apex and later repositioned in the coronary sinus. Standard recording and stimulating studies were performed, including description of anterograde and retrograde conduction and refractoriness by atrial and ventricular rapid pacing and programmed extrastimulation. Extrastimuli were delivered singly and in pairs during sinus rhythm and at multiple drive rates to the right atrium, coronary sinus, and right ventricle to induce supraventricular tachycardia. Unfortunately, no induced episodes were sufficiently prolonged to permit assessment of the effect of premature atrial or ventricular stimulation upon the tachycardia.

INTERPRETATION OF ELECTROPHYSIOLOGICAL RECORDINGS

Recordings during spontaneous sinus rhythm were normal. The atrial and right ventricular effective

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*This work was supported in part by an NIH grant.

refractory periods, and anterograde atrioventricular nodal refractory periods were normal. The anterograde atrioventricular nodal refractory curve was smooth, without evidence for dual conduction pathways. Wenckebach atrioventricular nodal conduction block appeared at an atrial pacing cycle length of 380 ms. Ventricular pre-excitation could not be demonstrated during pacing at multiple rates from high right atrium, low right atrium, or coronary sinus. During right ventricular pacing, the retrograde atrial activation sequence was low-to-high right atrium, and the right ventricular to low right atrial conduction time remained short and almost constant (90 to 105 ms) at all ventricular pacing rates to a maximum of 150 beats per minute (Fig. 1). In addition, during right ventricular extrastimulation (minimum V1 V2 achieved = 300 ms) the retrograde conduction time increased by only 15 ms. It is conceivable that greater retrograde conduction delay might have been found if the ventricle had been paced at rates greater than 150 beats per minute, or if right ventricular extrastimulation had been performed at rapid ventricular drive rates. Supraventricular tachycardia was easily and repeatedly induced with single or pairs of premature right atrial and coronary sinus extrastimuli. These tachycardias often followed induced single sinus node re-entrant beats (Fig. 2 and 3). The cycle length of supraventricular tachycardia was 330 ms. The atrial activation sequence was reversed (low right atrium to high right atrium). The coronary sinus electrogram followed the low and preceded the high right atrial signal. The AH interval during tachycardia was long, the QRS morphology unaltered, and the HV interval remained constant during most episodes.

The data reported so far suggest the presence of a concealed retrograde bypass short-circuiting the atrioventricular node. As judged from the retrograde atrial activation sequence, the atrial end of the fibre is right-sided. The origin of the ventricular end of the fibre cannot be determined precisely from the data presented so far, though the distal connection must be at or below the end of the atrioventricular node to explain the constancy of ventriculoatrial conduction time. Spontaneous episodes of infra-Hisian Wenckebach block during re-entry help us to localise the distal insertion of this fibre (Fig. 2 and 3). In the episode illustrated in Fig. 2, a premature right atrial stimulus leads to a sinuatrial nodal re-entry beat, after which re-entrant supraventricular tachycardia with reversed atrial activation sequence ensues (beats 4 to 6 in Fig. 2). During the tachycardia infra-Hisian Wenckebach block occurs. The HV interval associated with QRS complex beat 2 is normal (45 ms). The HV interval of the premature beat 3 is increased to 90 ms. On subsequent beat 4, the HV interval becomes normal after a pause caused by atrioventricular nodal conduction delay. The HV interval is increased again with the next cycle (beat 5) and complete block below the His occurs between beats 5 and 6. The HV interval is normal again on the sixth and seventh beats. The most important findings here are that: (1) ventriculoatrial conduction time remains constant despite HV interval

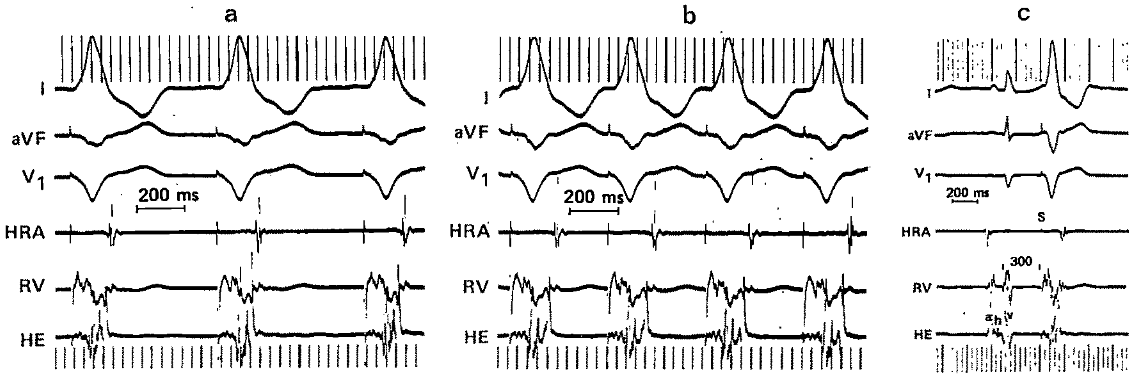

Fig. 1 *Surface electrocardiographic leads I, aVF, and V1 are recorded with three intracardiac electrograms. The boldest vertical time lines indicate one second intervals, and the lines of lesser boldness correspond to 200 and 40 ms intervals. The high right atrium (HRA), right ventricular inflow (RV), and His bundle (HE) electrograms are shown recorded at paper speeds of 50 and 100 mm/s. In* (a) *right ventricular apical pacing at a cycle length of 600 ms results in a short ventriculoatrial conduction time (90 ms) measured from the beginning of the right ventricular electrogram to the beginning of the low atrial electrogram in HE. With a decrease in pacing cycle length to 400 ms* (b) *there is a slight increase in ventriculoatrial conduction time to 100 ms. In* (c) *the maximally premature ventricular extrastimulus (V1V2 = 300 ms) fails to prolong ventriculoatrial conduction time.*

prolongation while HA time varies; and (2) retrograde atrial activation remains intact despite infra-Hisian block. The former finding rules against the possibility of a James bypass fibre inserting in the distal atrioventricular node or the atrioventricular nodal-His bundle junction, since a constant retrograde conduction time between His and atrium would have been recorded. The second finding eliminates the possibility of a septal Kent fibre, since ventricular activation was not required between beats 5 and 6 to maintain the ventriculoatrial limb of the re-entry circuit. In the ladder diagram (Fig. 2 and 3) in which an upper His bundle (UH) and a lower His bundle (LH) are depicted for illustrative purposes, the upper His bundle is assumed to be the region responsible for generation of the His spike, and the lower His bundle the site of infra-Hisian conduction delay and eventual block. It is in this lower region of the His bundle, just before the branching portion of the His-Purkinje system, where the bypass fibre's distal end seems to communicate with the conduction system. For maintenance of a constant ventriculoatrial time, the distal insertion of the bypass fibre in the bundle of His must be beyond the site of HV conduction delay, but above the site of conduction block.

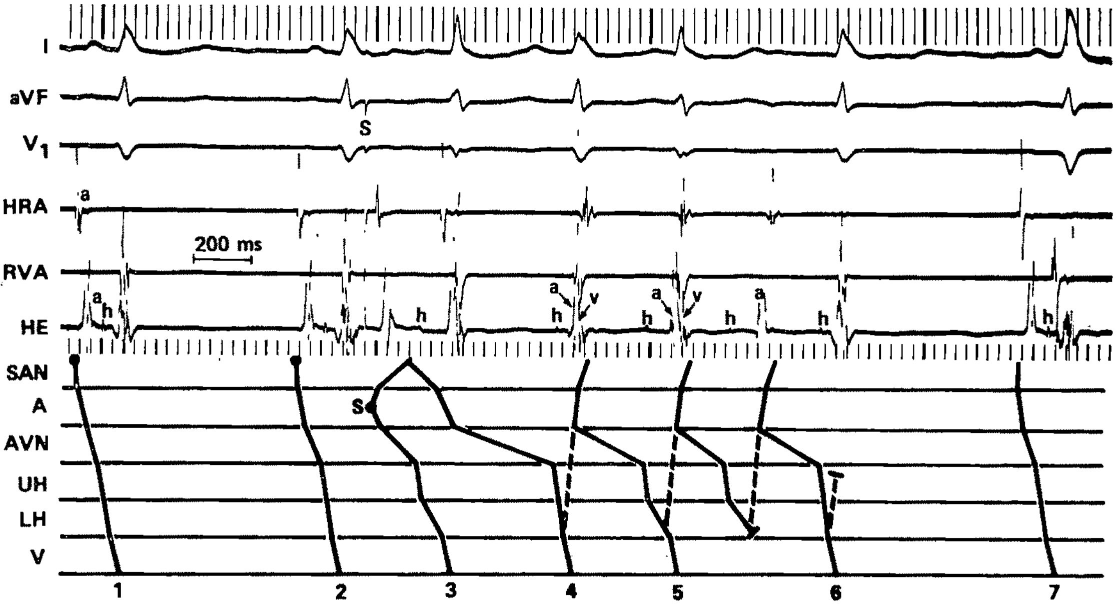

Fig. 2 *This illustration supplies evidence for the location of the input end of the concealed ventriculoatrial bypass fibre. The same surface and intracardiac leads shown in the previous illustrations are displayed, with a ladder diagram below the electrophysiological recordings. In the ladder diagram: SAN, sinuatrial node; A, atrium; AVN, atrioventricular node; UH, upper His bundle; LH, lower His bundle; V, ventricle. The first and second ventricular beats are of sinus origin. A single premature stimulus delivered to the high right atrium produces prolongation of both the AH and HV intervals and results in ventricular complex 3, via anterograde conduction. An atrial echo beat follows, presumably as a result of sinuatrial nodal re-entry, suggested by maintenance of the same high to low atrial activation sequence and atrial electrogram morphology seen in the previous sinus beats. With this atrial repetition pronounced lengthening of the AH interval occurs, HV interval prolongation disappears, and QRS 4 results. Another atrial repetition immediately follows the onset of ventricular complex 4, with low to high atrial activation. This represents the first of a three-beat run of re-entrant supraventricular tachycardia using the proposed atrio-His bypass. The second beat (QRS 5) of this supraventricular tachycardia is identical to the first beat, except that there is HV interval prolongation (from 45 to 90 ms). Note that the 45 ms prolongation of HV interval with this beat was* not *associated with any change in ventriculoatrial timing. A His electrogram is recorded after beat 5, but no ventricular electrogram or QRS follows. However, the third atrial beat of the three-beat run occurs despite the infra-His block. It should be noted further that the HA conduction time is inconstant during all three beats of supraventricular tachycardia. QRS complex 6 is the last one generated by the run of supraventricular tachycardia. Tachycardia is interrupted because of failure of retrograde atrial capture after QRS 6. Thus, these recordings show a run of supraventricular tachycardia with retrograde atrial activation, infra-His Wenckebach block, inconstant HA conduction time, and constant ventriculoatrial conduction time, with preservation of atrial activation despite failure of ventricular capture. Mild terminal QRS aberrancy occurs in beats 3 and 5, both of which show HV interval prolongation.*

Fig. 3 is provided to show the presence of a critical AH delay as a requirement for induction of supraventricular tachycardia in this patient. This lends support to the hypothesis that a mechanism of re-entry is responsible for the arrhythmia.

One additional explanation for these findings should be considered. It is conceivable that the site of re-entry actually existed in the atrioventricular node, and that constancy of ventriculoatrial conduction times and inconstancy of HA conduction times were accounted for by, coincidentally, exactly opposite changes in retrograde atrioventricular nodal and anterograde HV times from beat to beat. This seems an unlikely explanation, because it requires an improbable coincidence. The presence of fixed ventriculoatrial conduction time during ventricular pacing strongly favours a non-AV nodal pathway serving as the retrograde limb of the re-entry circuit.

If we conclude that the ventricular end of the bypass fibre cannot terminate in the atrioventricular node or the proximal His bundle, one other possibility must be considered: distal termination on the right or left proximal bundle-branch. Such a fibre could account for all of the electrophysiological findings presented. But, in order for

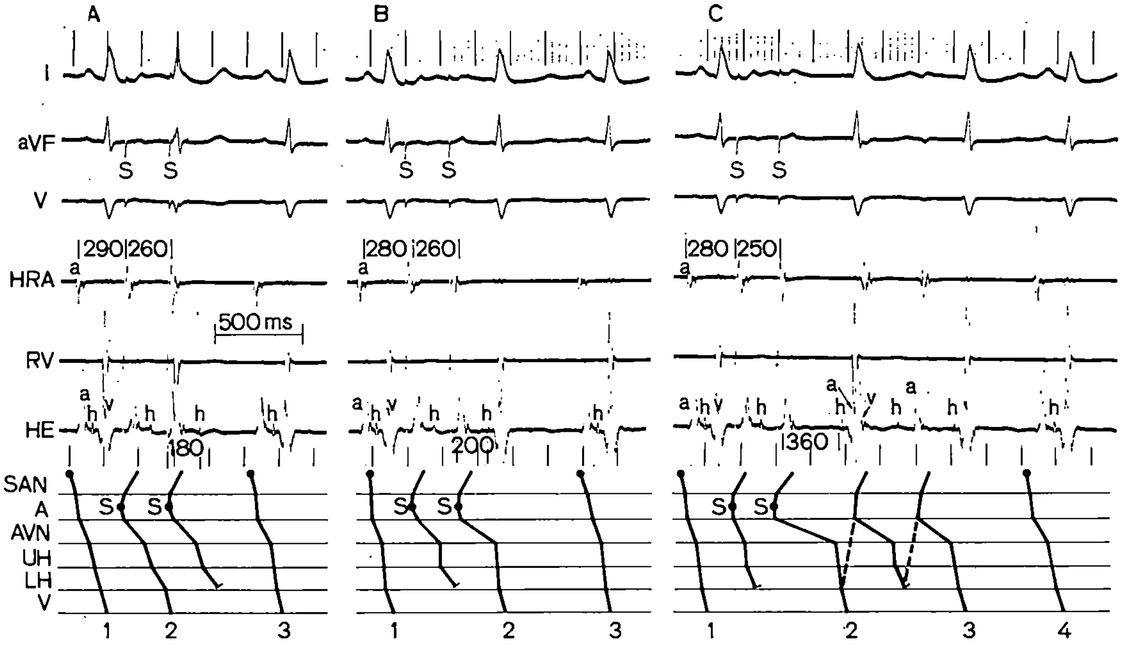

Fig. 3 *The illustration shows that a critical atrioventricular noda lconduction delay is required for the proposed re-entrant phenomenon to occur. In each of the three panels, surface electrocardiographic leads I, aVF, and V1 are displayed with the high right atrial, right ventricular, and His bundle electrograms, and explanatory ladder diagrams appear below each panel. Abbreviations are the same as those used in Fig. 2. In each of the three illustrations, a pair of atrial extrastimuli is delivered during sinus rhythm. In* (A) *the first extrastimulus (labelled* S*) is delivered 290 ms after the last spontaneous atrial complex and results in minimal AH prolongation and considerable HV prolongation from 45 to 90 ms. The second extrastimulus, also labelled* S*, occurs 260 ms after the previous one and results in further AH prolongation to 180 ms, followed by infra-Hisian conduction block.*

In (B) *the first stimulus is moved 10 ms closer, which results in a further small increase in AH interval, and infra-Hisian conduction block. The second extrastimulus remains 260 ms after the first, and the resultant AH interval is increased to 200 ms. His ventricular conduction is intact, but no re-entry is seen.*

In (C) *the first extrastimulus is kept 280 ms after the last spontaneous beat and again results in infra-Hisian conduction block. The second extrastimulus is moved 10 ms closer to the first stimulus, resulting in an increase in AH conduction time to 360 ms. This degree of atrioventricular nodal conduction delay results in re-entry and retrograde atrial activation. When this first atrial echo (after QRS complex 2) re-enters the conduction system anterogradely, infra-Hisian block again occurs, but the re-entry phenomenon then terminates with retrograde block. With the same premature stimulus intervals, AH delays between 200 and 360 ms were achieved without appearance of re-entry. Thus, a critical degree of AV nodal conduction delay was required for the echo phenomena, supporting the previous conclusion that re-entry is involved.*

such a fibre to be re-entered during the episode of infra-Hisian Wenckebach block (Fig. 2 and 3), one would have to require that the anterogradely propagated impulse went beyond the bifurcation point of the proximal bundle-branch system, entered the retrograde bypass fibre, and then was blocked in both distal bundle-branch systems before activation of any ventricular myocardium.

Discussion

Convincing electrophysiological evidence for concealed atrioventricular bypass pathways—that is, channels bypassing portions of the atrioventricular conduction system and capable of conducting only in the retrograde, ventriculoatrial direction—has been presented in the past four years.[4–7] In 1974, Narula pointed out that unidirectional retrograde atrioventricular nodal bypass circuits were present in a surprisingly high proportion (at least 15%, and, perhaps, as much as 47%) of patients with demonstrable ventriculoatrial conduction.[4] More recently, Sung[7] and Gillette[6] and their collaborators have established that many patients with re-entrant supraventricular tachycardia utilised concealed retrograde atrioventricular bypasses for initiation and maintenance of their re-entrant supraventricular arrhythmias.

While the absence of typical atrioventricular nodal delay during ventriculoatrial conduction suggests a *functional* bypass of the atrioventricular node, the anatomical substrait for this physiological finding is uncertain. The atrial fibres described by James,[3] which circumvent portions or all of the atrioventricular node to terminate at the atrioventricular nodal-His bundle junction or at the base of the tricuspid valve, might possibly function as unidirectional ventriculoatrial communications, with rapid, non-decremental conduction. A physiological-pathological correlation has not been performed, and would be nearly impossible to achieve. In two reports, Brechenmacher described atrioventricular bypass fibres coursing through septal tissue to connect the atria with the bundle of His.[1 2] He pointed out that direct atrio-His connections could be differentiated from the fibres of James by virtue of their direct communication with the bundle of His rather than the distal atrioventricular node or the nodal-His junction. Brechenmacher considered these atrio-His bridges to be relatively rare, and could present only circumstantial evidence for a functional significance of the fibres.

On superficial examination of the recordings herein, several explanations for the data might seem tenable. Among these possibilities are: (1) a James fibre terminating at the lower portion of the atrioventricular node; (2) a James fibre terminating at the atrioventricular node-His bundle junction; (3) a septal Kent fibre; and (4) a typical atrioventricular nodal re-entrant phenomenon. Arguments against these possible explanations have been offered. Electrophysiological findings in this report suggest unidirectional retrograde ventriculo-atrial bypass physiology best explained by the presence of an atrio-His bypass fibre similar to the second case of Brechenmacher[2] in which the fibre inserts into the *distal* His bundle just above its branching point.

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Br Heart J 1980; **43:** 605–6

Truncus arteriosus communis with intact ventricular septum

Sir,

We read with attention the paper by Carr *et al.* entitled "Truncus arteriosus communis with intact ventricular septum".[1] The authors document clinically and pathologically a patient with truncus arteriosus communis in which the ventricular outflow tracts were completely separate below a common semilunar valve. The case furnishes evidence that the presence of an infundibular septal defect is not essential in defining truncus arteriosus communis, and otherwise suggests that the septation of the cardiac outflow tracts comes from distinct development of conal, truncal, and aortopulmonary septa.

These concepts had been clearly underlined in our recent paper.[2] The spectrum of malformations illustrated by Carr *et al.*[1] in their Fig. 6 corresponds to the one schematically anticipated by us. Indeed, the case reported by these authors had been foreseen in Fig. 11 of our paper as "absent truncal and aortopulmonary septa with normally developed conal septum (not described so far)".

We regret that our contribution, though published in the *British Heart Journal,*[2] has not been quoted. Using Dr Bharati's own words[3] we would suggest, "to read the literature carefully and include the previous work done by other people. This may perhaps help to write a paper in an objective manner".

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This letter was shown to Dr Carr and his colleagues who reply as follows:

We have long enjoyed the contributions to the journals made by Drs Thiene and Bortolotti and look forward to doing so in the future. We are unable to share their wish that we had quoted them in our paper and we do not agree with the three reasons for doing so that they have given. Like ourselves, Thiene *et al.* cannot claim originality for any of the concepts common to both papers. Every malformation contained in the spectrum illustrated in our paper had been described by other authors, not only previous to our own paper, but also previous to the paper by Thiene *et al.* (which described a theoretical spectrum, not restricted to hearts that had already been described). Finally, the idea of truncus arteriosus without ventricular septal defect is not a new one, for example.[1] Cases such as ours had been reported by other authors before Thiene *et al.* restated the possibility of their existence. These facts are clear from the references we cited.

Translating into the terminology used by Thiene *et al.*, our paper corroborates the concepts[2] that absence of septation of the ventricular infundibulum is *not invariable,* that *not all* types of truncus arteriosus should be considered as a single undivided conotruncus, and that the only necessary condition for the diagnosis of truncus arteriosus is a single semilunar valve common to both ventricles (and we should add, common to both great arteries). Thiene *et al.* reached the opposite conclusion; we quote from their Summary: "*The invariable absence of septation of the ventricular infundibulum* and semilunar valve, in spite of the variable anatomy of the free wall of the conus, indicates that *all types of truncus arteriosus,* ontogenetically, *should be considered as a single undivided conotruncus*" (emphasis added).

Our paper described a single heart, not the first of its kind to be reported, but the first of its kind on which there was so much information. We showed how this heart corroborated concepts expressed by previous authors. Had we, instead, written an exhaustive review of the subject we would then have included the citation of their paper.

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Br Heart J 1980; **43**: 607–8

Development of the membranous septum in the human heart

Sir,

I have read the interesting morphological work by Drs Allwork and Anderson (*Br Heart J* 1979; **41**: 275–80) and congratulate them on it. As far as the manner of development of the two parts of the membranous septum is concerned, their results confirm my findings on the development of the Chiroptera heart,[1] which have been quoted by Patten.[2] As regards the human heart my conclusions were that "the two components (ie the interventricular and the atrioventricular) of the membranous septum in man—as in Chiroptera—have a single subendocardiac origin, in consequence of the formation of the septal leaf of the tricuspid valve and have no connection either with the bulbar septum or with the ventricular foramen".[3]

However, I disagree with the opinion of Drs Allwork and Anderson, concerning the time at which these two components of the membranous septum develop. I found, both in Chiroptera and human hearts, that the two parts of the membranous septum always develop before birth.[1 3] In fact, in the human heart the myoendocardial undermining which moulds the septal leaf of the tricuspid valve begins in 30 to 47 mm long fetuses (approximately three months old). At 5 months the same septal leaf arises from the caudal margin of the membranous septum which is thus as yet wholly atrioventricular. Perhaps the small number of fetuses led the authors to miss later developmental ages which are enlightening. Unpublished observations show that in the hearts of 6- and 7-month-old fetuses the undermining goes on and the septal leaf at this age arises from the membranous septum dividing it into atrioventricular and interventricular parts. In the 8- and 9-month-old fetuses and in newborns both of the membranous parts grow thinner and become more dense. Therefore, contrary to Allwork and Anderson's opinion, these two parts are already distinct long before birth.

According to Savary[4] (and in my experience) the relative sizes of the two components are inversely proportional to each other, with individual variations. Perhaps the variations in the level of insertion of the right septal leaf are connected with the mechanical effect of haemodynamics on the embryonal (and, therefore, easily undeterminable) connective tissue of the membranous septum. If this undermining stops at the caudal margin of the embryonal membranous septum this remains entirely atrioventricular (as in two of the seven adult Chiroptera hearts I examined[1]); if the undermining stops at the level of the embryonal membranous septum, this will show the two typical components; when the undermining concerns the whole embryonal membranous septum up to its cranial margin it will become entirely interventricular. These findings agree with Savary's reports that the membranous septum was wholly atrioventricular in 4 per cent, wholly interventricular in 10 per cent, and divided into atrioventricular and interventricular parts in 86 per cent of the adult human hearts examined.

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Istituto di Anatomia Umana
Normale, dell'Università di
Pisa, Pisa, Italy.

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[4] Savary M. Beitrag zur Kenntnis des Septum membranaceum cordis. Untersuchung an 167 menschlichen Herzen. *Acta Anat (Basel)* 1964; **59**: 333–60.

This letter was shown to Drs Allwork and Anderson who reply as follows:

Sir,

We read Dr Conte's comments with interest, especially his observations on the heart of the bat. However, it seems to us that it is probably inappropriate to interpret the findings in one species in the light of those in another disparate animal.

Dr Conte's finding that some fetal and neonatal hearts possess both components of the membranous septum, endorses rather than disagrees with our observations. In our series the *majority* of young hearts had only an atrioventricular membranous septum, but we noted and illustrated hearts with both (our Fig. 3a and b).

We agree with Dr Conte that the process whereby the membranous septum attains its adult morphology and size depends upon the emancipation of the medial tricuspid leaflet from the muscular septum. We illustrated the variable timing of this event in Fig. 2 and 3. Our Fig. 7 suggests that this "modelling" process may be lifelong, but we have reservations about attributing this or any other developmental process to haemodynamics.

S P Allwork,
R H Anderson,
Royal Postgraduate Medical
School, Hammersmith
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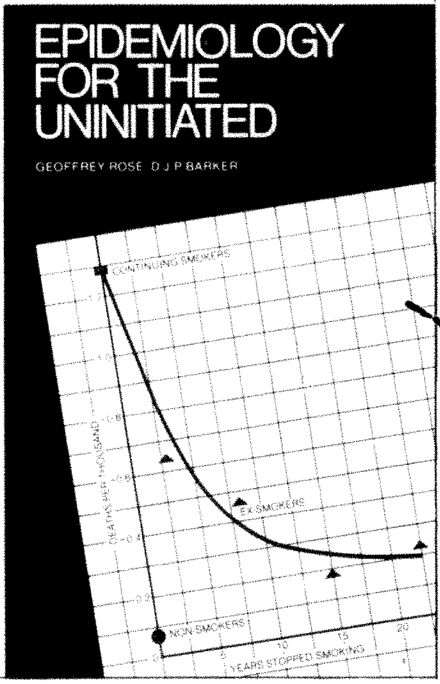

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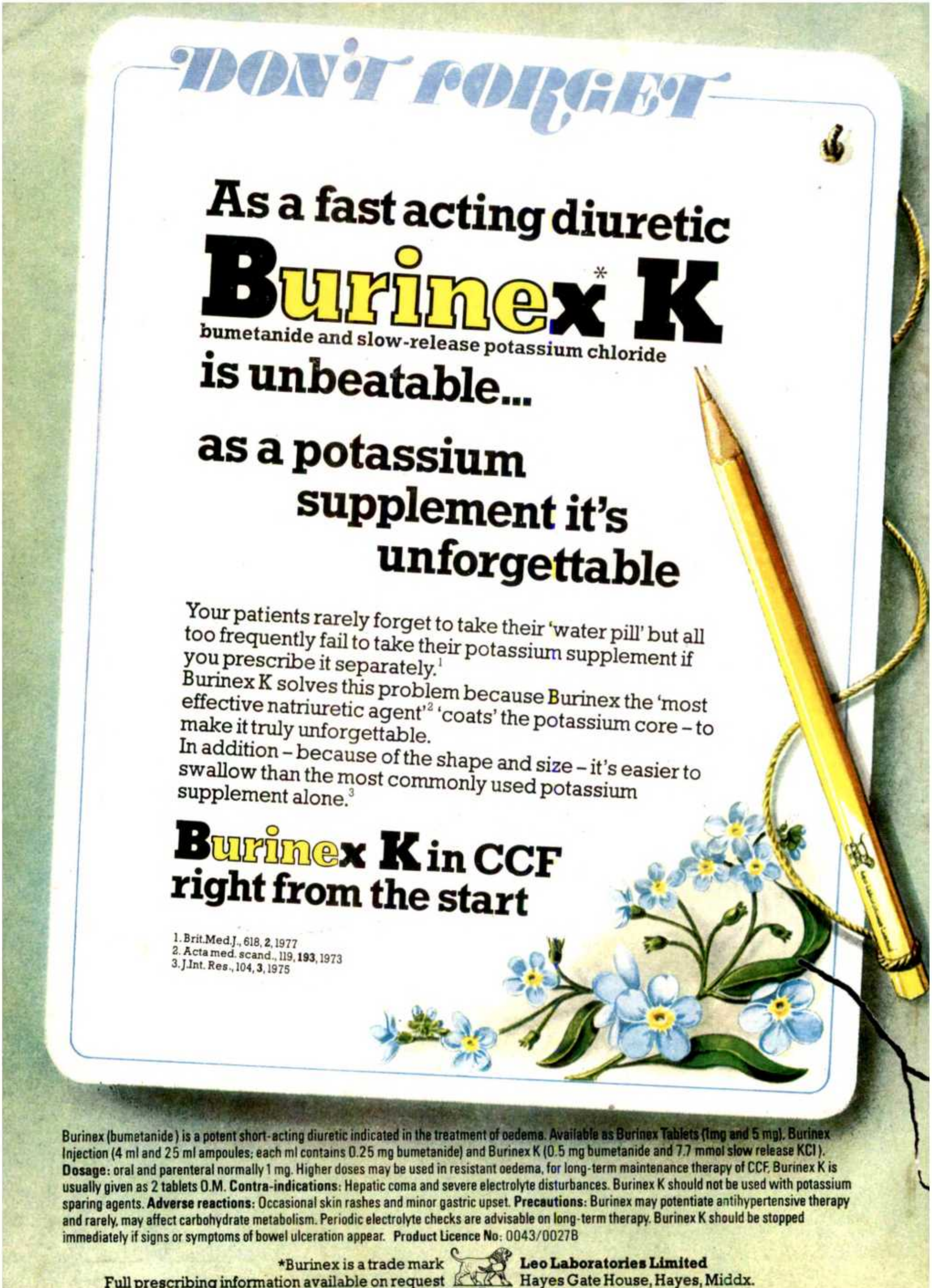

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(2) *Books and other monographs:*
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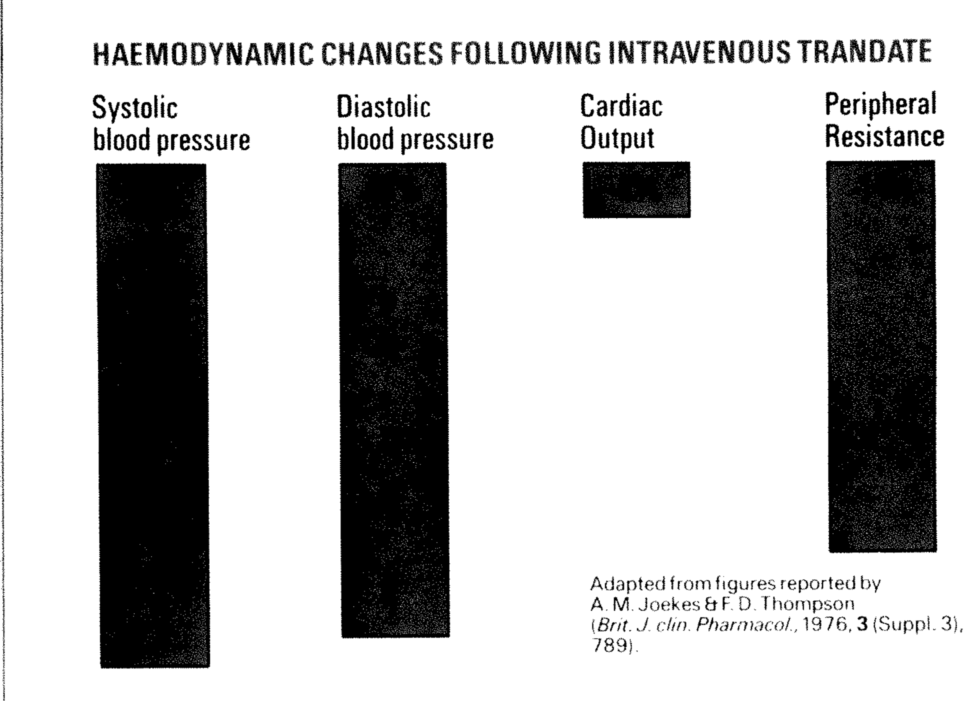

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PRESENTATION
Trandate Tablets 100mg, 200mg and 400mg each contain labetalol hydrochloride, 100mg, 200mg and 400mg, respectively. In packs of 50 and 250. PL 0045/0106, PL 0045/0107 and PL 0045/0109.
Trandate Injection: 20ml ampoules each containing 100mg (5mg/ml) labetalol hydrochloride. In boxes of 5 ampoules. PL 0045/0104.

INDICATIONS
Trandate Tablets are indicated for the oral treatment of all grades of hypertension, mild, moderate and severe.
Trandate Injection is indicated when rapid control of blood pressure is essential.

DOSAGE AND ADMINISTRATION
Trandate Tablets:
Adults: The initial dosage should not usually exceed 100mg 3 times daily. Adjustment of dosage should be gradual. Most cases are controlled with 600mg per day or less, but severe cases may require up to 2,400mg daily. Administration should be after a main meal.
Trandate Injection:
Adults: When rapid reduction of blood pressure is essential a dose of 50mg of Trandate should be given by intravenous injection over at least one minute. This may be repeated, if necessary, at 5-minute intervals but the total daily dose should not exceed 200mg. Alternatively it may be given by intravenous infusion. For this 2 ampoules of Trandate Injection are diluted to 200ml with sodium chloride and dextrose injection BP. This is infused at a rate of 2ml/minute until a satisfactory response is obtained when the infusion should be stopped. For most patients the effective dose is from 50 to 200mg but in phaeochromocytoma up to 300mg may be necessary.
Patients should be in the supine position when Trandate Injection is given and they should not stand or sit up within 3 hours of starting the administration. Once controlled, blood pressure reduction can be maintained with Trandate Tablets at a starting dose of 200mg 3 times daily.
Children: Not applicable.
For information on the use of Trandate with other drugs or for transfer to Trandate from other antihypertensive agents, see respective Data Sheets.

CONTRA-INDICATIONS, WARNINGS, ETC.
Trandate should not be given to patients with uncontrolled or digitalis-resistant heart failure, or with atrioventricular block. Caution is necessary in asthmatic patients or others prone to bronchospasm. Patients with severe liver damage will probably require lower doses of Trandate than usual. Unnecessary administration of drugs during the first trimester of pregnancy is undesirable.
Trandate Injection may cause excessive postural hypotension if patients are allowed to assume the upright position within 3 hours of administration.
Trandate Tablets may cause symptoms of postural hypotension if initial dosage is too high or increased too rapidly, but they are uncommon, except at very high doses, if used as recommended. Mild and usually transient side effects include: headache, tiredness, dizziness, depressed mood, lethargy, difficulty in micturition, epigastric pain and nausea and vomiting. Tingling in the scalp has occasionally occurred but is usually transient. Rarely, a lichenoid rash has been reported which disappears on drug withdrawal. Other skin rashes, blurring of vision, eye irritation and cramps have been reported but have been difficult to relate directly to Trandate treatment.
Warning: There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenoceptor blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the drug was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable. Cessation of therapy with a beta-adrenoceptor blocking drug should be gradual.

A UNIQUE PROFILE IN HYPERTENSION

Full prescribing information is available on request.

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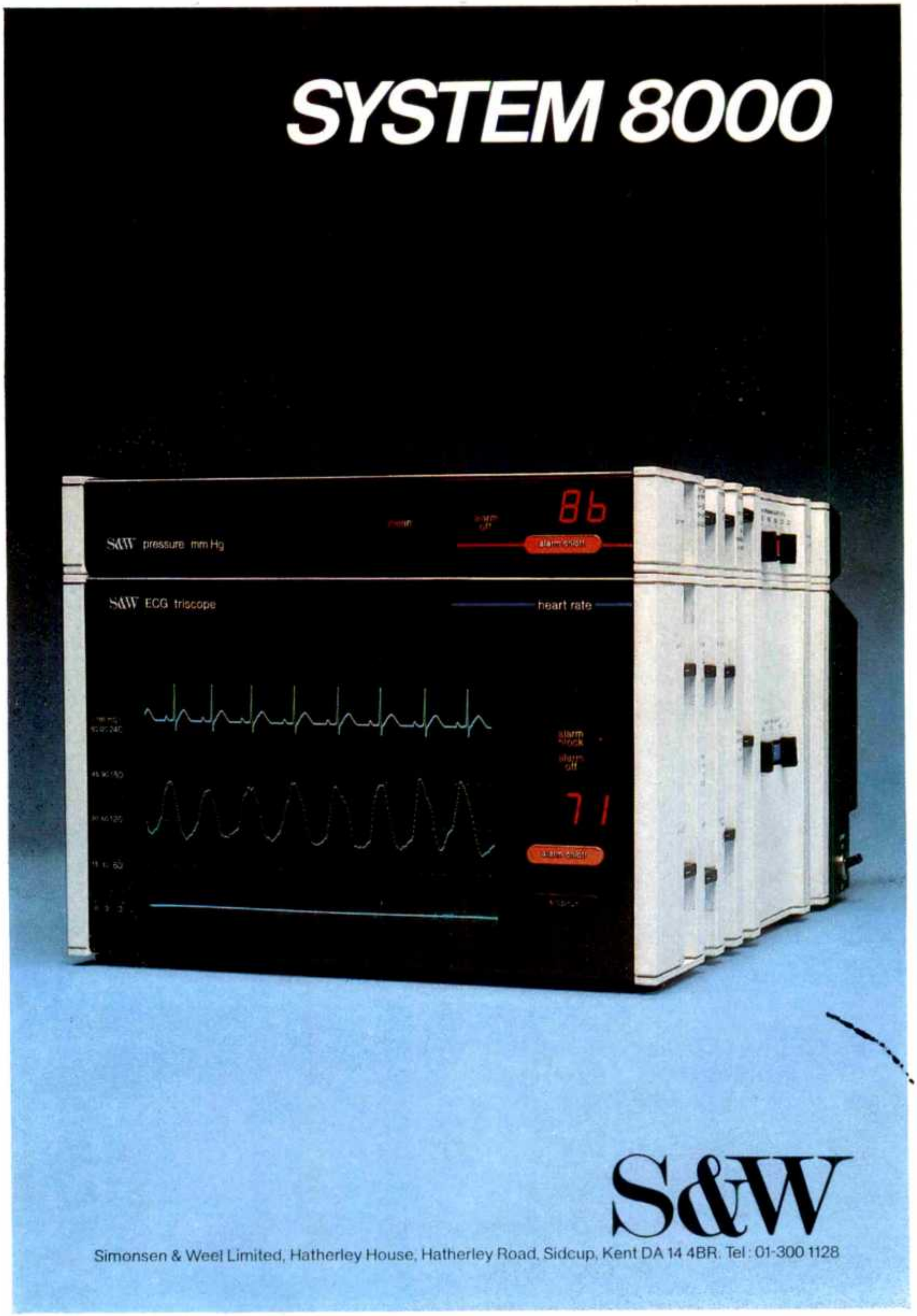

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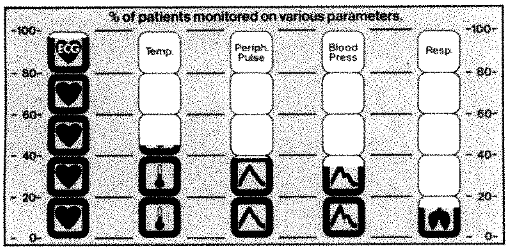

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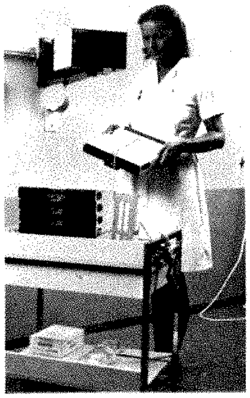

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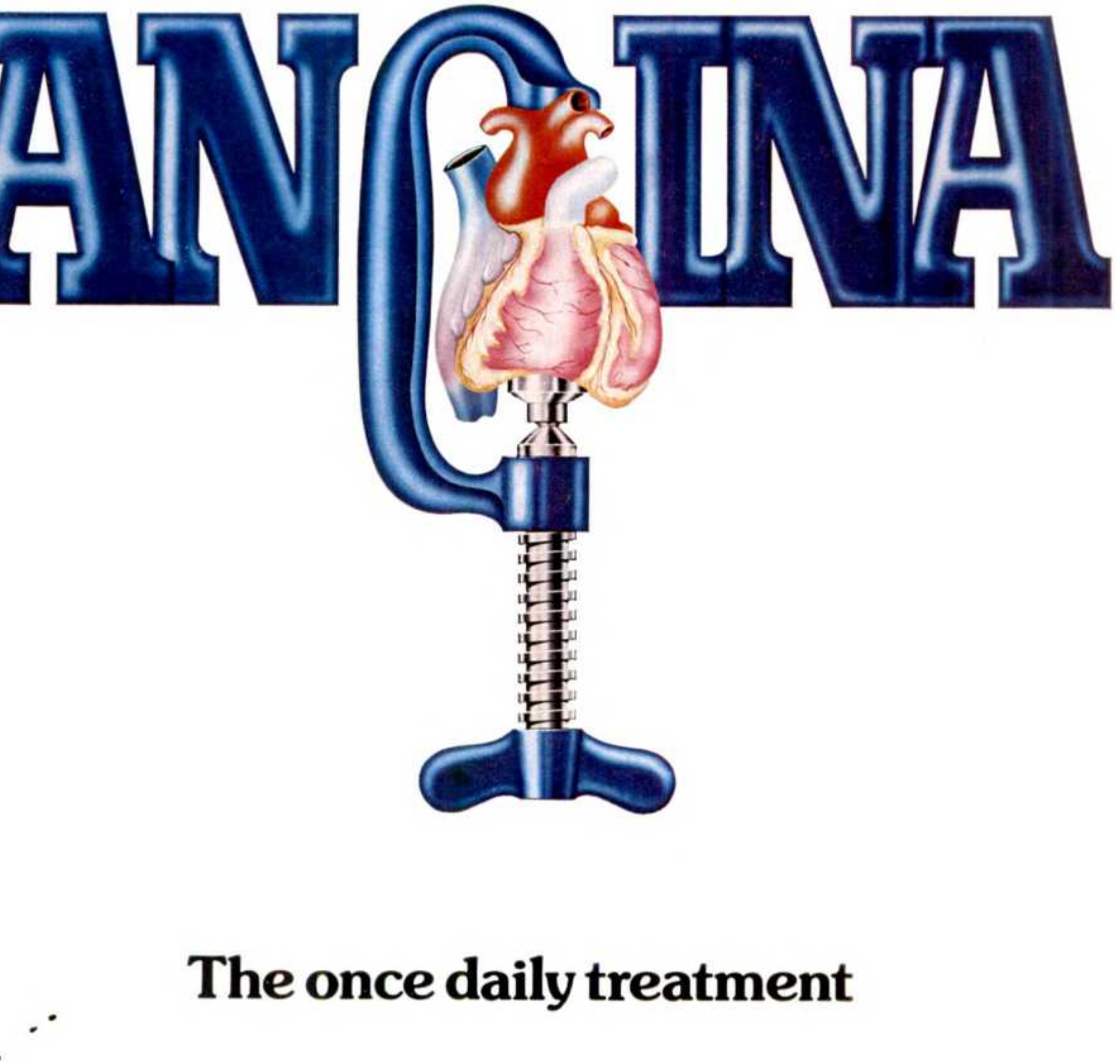

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Prescribing Notes:
Presentation Slow-Trasicor tablets each contain 160mg oxprenolol hydrochloride BP in a special sustained-release formulation available in simple daily reminder packs of 28 tablets. **Dosage in hypertension** Initially one or two tablets in the morning. **Dosage in angina** Initially one or two tablets in the morning. An evening dose may be beneficial in nocturnal angina. As with other beta-blocking drugs, sudden withdrawal of treatment may induce severe and continuous angina. Patients should, therefore, be advised to avoid interruption of established therapy and if withdrawal becomes necessary it should be done gradually. **Side effects** Dizziness, drowsiness, headache, insomnia, excitement and gastro-intestinal disturbance may occur and, rarely, isolated cases of excessive bradycardia. Beta-blockers are occasionally associated with skin rashes and/or dry eyes. If any such reaction is suspected, treatment should be withdrawn gradually. **Precautions** If there is evidence of cardiac failure this must be controlled by digitalis and/or diuretics before and during Slow-Trasicor therapy. Should the pulse rate fall below 50 per minute, then treatment should be restarted at a lower dose. Caution should be observed when treating asthmatics, chronic bronchitics or other individuals where bronchospasm may be provoked. Slow-Trasicor should be given cautiously to patients with alcoholism, metabolic acidosis, during pregnancy or anaesthesia with ether or chloroform. Beta-blockers can mask symptoms of hypoglycaemia and also affect carbohydrate metabolism. It may therefore be necessary to readjust the insulin requirements in diabetic patients. Occasionally hypotension may occur with higher dose levels. **Contra-indications** Patients with atrio-ventricular block, marked bradycardia and cardiogenic shock. **Packs** Cartons of 28 Slow-Trasicor tablets consisting of two reminder calendar foils of 14. Basic NHS price £6.66 PL0008/0130 PA 28/7/1 Full prescribing information is available on request from CIBA Laboratories, Horsham, West Sussex.
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CONTRA-INDICATIONS, WARNINGS ETC.
NORPACE is contra-indicated in patients with second or third degree AV block if no pacemaker is present, cardiogenic shock and hypersensitivity to disopyramide phosphate.
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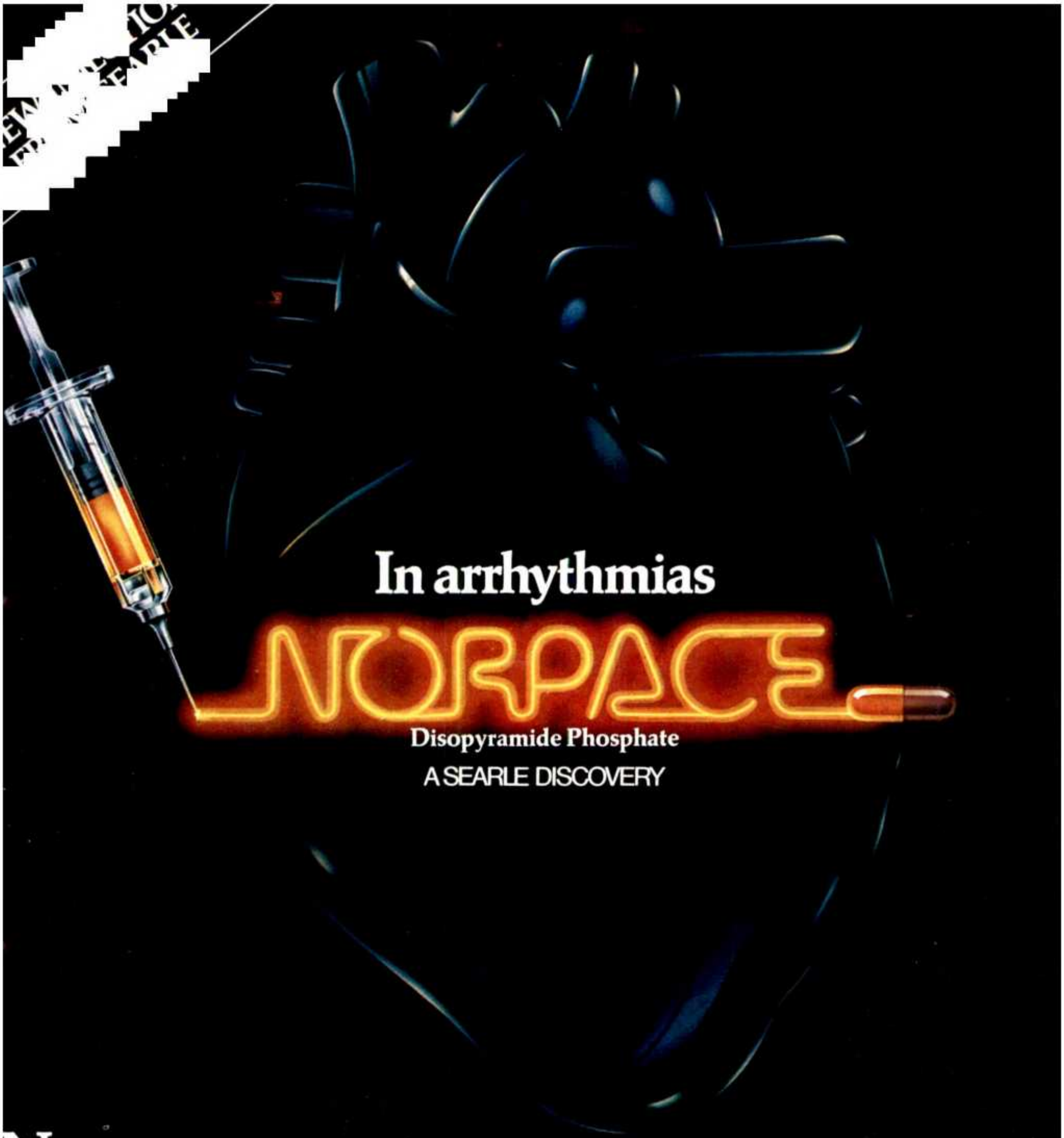

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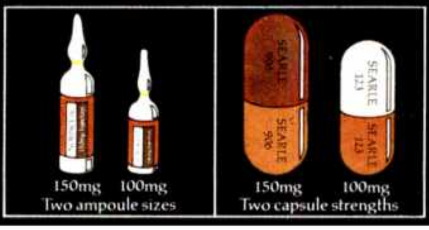

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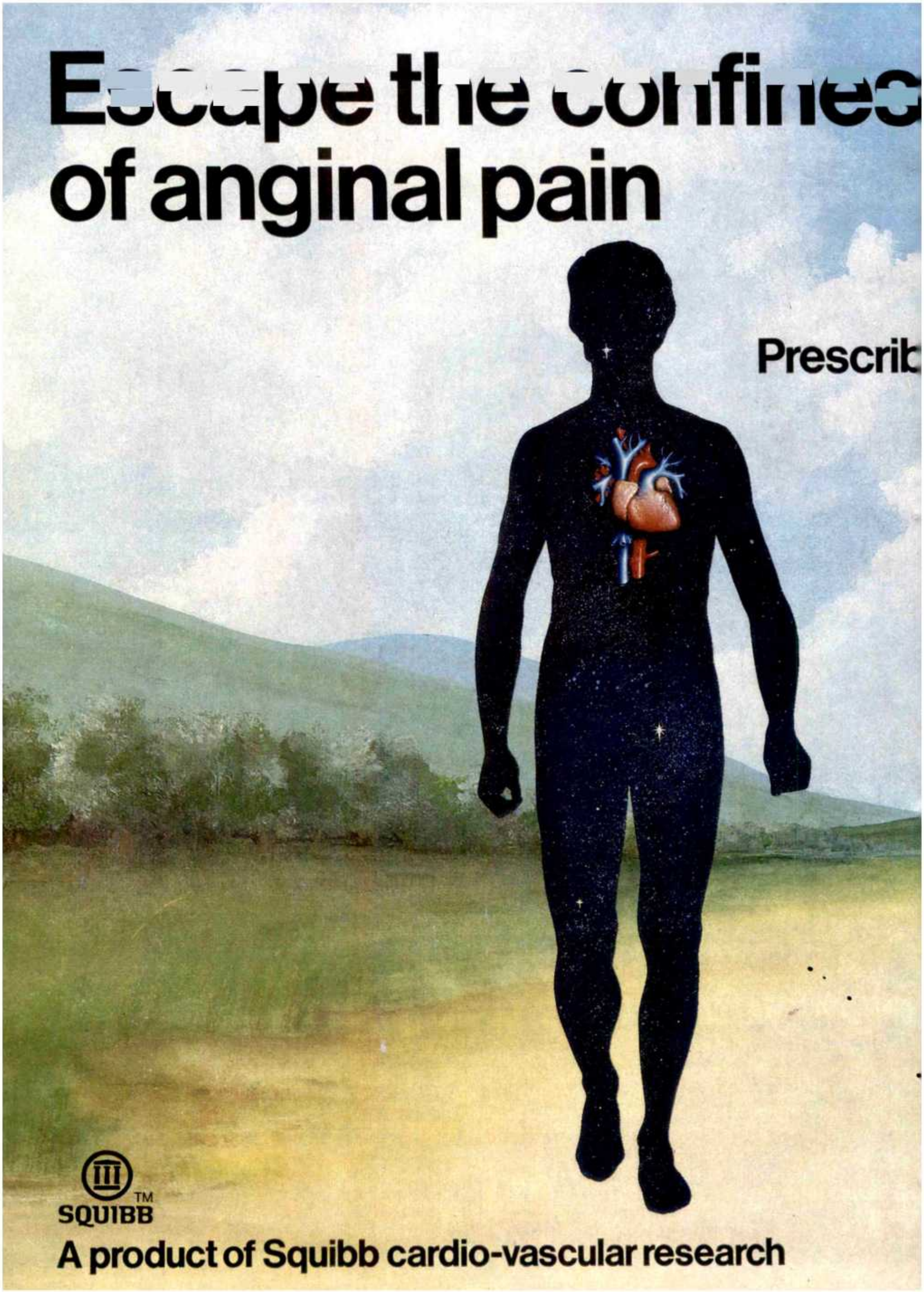
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Indications
Corgard is indicated in the long-term management of angina pectoris and hypertension.

Dosage and administration
Dosage should be individually titrated. In elderly patients, particularly those with angina pectoris, a low initial dose should be used so that sensitivity to side effects may be assessed.

Nadolol may be given in a once daily dosage without regard to meals.

Angina Pectoris: Initially 40 mg once daily. This may be increased at weekly intervals until an adequate response is obtained or excessive bradycardia occurs. Most patients respond to 160 mg or less daily.

The value and safety of daily doses exceeding 240 mg have not been established.

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Treatment of hypertension associated with phaeochromocytoma may require the addition of an alpha-blocking agent.

Contra-indications
Bronchial asthma, sinus bradycardia and 2nd and 3rd degree heart block, cardiogenic shock; right ventricular failure secondary to pulmonary hypertension; congestive heart failure.

Warnings
The normal precautions associated with the use of beta-adrenergic blockers should be followed.

Exacerbation of angina and myocardial infarction have occurred after abrupt discontinuation of therapy with beta-adrenergic blocking agents in patients with angina pectoris or other evidence of coronary artery insufficiency.

When discontinuing long-term nadolol therapy the dosage should be reduced gradually over a period of at least two weeks.

There have been reports of skin rashes and/or dry eyes associated with the use of beta-adrenergic blocking drugs. The reported incidence is small and in most cases the symptoms have cleared when the treatment was withdrawn. Discontinuance of the drug should be considered if any such reaction is not otherwise explicable.

Caution is advised in the presence of impaired renal or hepatic function, obstructive airways disease and diabetes mellitus.

Care should be taken in administering nadolol during and within 2 weeks of administration of adrenergic augmenting psychotropic drugs such as monoamine oxidase inhibitors.

The safety of nadolol in pregnancy has not yet been established, and nursing mothers should only receive nadolol if deemed essential.

Side-effects
These resemble those reported with other beta-blocking drugs and rarely require withdrawal of treatment. Those reported infrequently include gastro-intestinal effects, bradycardia, fatigue, light-headedness, cold extremities, insomnia, paraesthesia and dryness of the mouth. Cardiac insufficiency, hypotension and AV block have occurred on rare occasions. Overdosage or exaggerated response should be treated supportively and symptomatically.

Legal category
Prescription only.

Product Licence Numbers
80 mg – 0034/0186
40 mg – 0034/0185

Package quantities
Bottles of 100 tablets.
Average daily cost of treatment 16p per day.

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Presentation Orange, soft gelatin capsule containing yellow viscous liquid. Each capsule contains 10mg nifedipine. **Uses** *Mode of Action* Adalat is a potent calcium antagonist. Its most important effect is to protect the heart against excessive oxygen utilisation during physical activity. There is a reduction in cardiac work and in myocardial oxygen demand. Adalat also causes peripheral vasodilatation and thus reduces peripheral resistance and heart work load. Adalat has no therapeutic anti-arrhythmic effect. Since Adalat does not cause a rise in intraocular pressure, it can be used in patients with glaucoma. *Indications* For the treatment and prophylaxis of angina pectoris. **Dosage and Administration** For oral administration, the capsules should be taken with a little fluid during or after meals. The recommended dose is one 10mg capsule three times daily. If necessary, up to two capsules three times daily may be taken. Treatment may be continued indefinitely. If an immediate effect is required, the capsule should be bitten open and the liquid contents allowed to remain in the mouth. **Contra-indications** Must not be given to women capable of child-bearing. **Warnings and Precautions** Adalat is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker, preferably over 8-10 days. Adalat may be used in combination with beta-blocking drugs and other antihypertensive agents, but the possibility of an additive effect resulting in postural hypotension should be borne in mind. Adalat will not prevent possible rebound effects after cessation of antihypertensive therapy. Adalat should be used with caution in patients whose cardiac reserve is poor. Ischaemic pain has been reported in some patients, commonly within 30 minutes of the introduction of Adalat therapy. Patients experiencing this effect should discontinue Adalat. The use of Adalat in diabetic patients may require adjustment of their control. There is no known drug incompatibility. **Side effects** Adalat is well tolerated. Minor side-effects, usually associated with vasodilatation are mainly headache, flushing and lethargy. These are transient and invariably disappear with continued treatment. **Overdosage** Standard measures such as atropine and noradrenaline may be used for resultant bradycardia and hypotension. Intravenous calcium gluconate may be of benefit. **Pharmaceutical Precautions** The capsules should be protected from strong light and must be stored in the manufacturer's original container. **Legal Category** POM. **Pack Quantities and Basic NHS Cost** Adalat is available in foil packs of 100 capsules. Daily treatment cost 36p (3 capsules ex 100). **Further Information** Nil. **Product Licence Number** PL0010/0021; Republic of Ireland: PA 21/3/1.

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Br Heart J 1980; **43:** 609–16

Comparison of enzymic with cineangiocardiographic estimations of myocardial infarct size*

N L SAMMEL, J G STUCKEY,† P W T BRANDT, R M NORRIS‡

From Green Lane Hospital, Auckland 3, New Zealand

SUMMARY Comparisons were made between enzymic indices of myocardial infarct size (total creatine kinase appearance and peak enzyme activity) measured during the acute stage of a first myocardial infarct in 32 male patients, and analysis of contraction abnormalities in biplane left ventricular cineangiocardiograms performed one month later. The cineangiocardiograms were analysed independently by two radiologists, each using two different methods for quantification of subjectively classified abnormalities of left ventricular wall motion. A very strong correlation was found between the two enzymic indices of infarct size and somewhat weaker correlations between assessment of contractility abnormalities made by the two radiologists using the same method, or by the same radiologist using the two different methods. Comparisons between enzymic and angiocardiographic indices for all infarcts showed correlation coefficients (r) within the range of 0·53 to 0·72. With all comparisons of enzymic with radiological indices r values were higher for anterior infarcts than for inferior infarcts, and there was a tendency for higher enzyme levels for a given degree of left ventricular damage in inferior than in anterior infarction. This may be the result of variable degrees of right ventricular damage in inferior infarction.

Mortality and morbidity after myocardial infarction are largely related to the extent of myocardial damage,[1] and in recent years have prompted the evaluation of methods to reduce infarct size in patients.[2–4] Estimation of cumulative creatine kinase appearance into the blood from an infarcted region (integral CK) is a common method for the assessment of myocardial damage and evaluation of therapeutic interventions.[2 5 6]

Most authors have reported a good correlation between myocardial damage as estimated by serum CK and other means, such as necropsy findings,[7] biplane cineangiocardiography,[8] and myocardial CK depletion in experimental myocardial infarction.[9 10] Criticism of integral CK, however, continues both regarding the assumptions made in its calculation[11 12] as well as its correlation with histological infarction size in experimental animals.[13]

Our study attempts to shed further light on the controversy by comparing infarct size measured by total CK appearance with peak CK activity, as well as with biplane cineangiocardiographic assessments of myocardial damage using subjective analysis of both the ventriculograms and coronary arteriograms.

Patients and methods

Thirty-eight consecutive male patients under 60 years of age seen within 12 hours of the onset of symptoms of an uncomplicated first myocardial infarct were entered in the study. Seven patients were subsequently excluded after analysis of left ventriculography and coronary arteriography In two, the left ventriculogram was technically unsatisfactory, and in five previous myocardial infarction could not be excluded in the presence of either two separate areas of left ventricular dysfunction (two patients) or a single abnormal region supplied by more than one occluded vessel (three patients). Our findings refer to the remaining 31 patients. Management in the coronary care unit was of a routine nature with the administration of antiarrhythmic drugs (usually lignocaine), frusemide, and analgesics (usually papaveretum) when necessary. Some patients were included in the continuation of a clinical trial of propranolol in acute myocardial infarction.[6] No drugs were given intramuscularly, and patients undergoing cardio-

---

* This work was supported by the Medical Research Council and The National Heart Foundation of New Zealand.

† Present address: Department of Radiology, Royal Melbourne Hospital, Victoria 3050, Australia.

‡ Present address: Department of Cardiology, The Radcliffe Infirmary, Oxford OX2 6HE, England.

Received for publication 8 October 1979

version were excluded from the study. Blood for CK sampling was withdrawn from an intravenous cannula inserted at the time of admission. Sampling was performed four-hourly for 72 hours or until CK, as measured by the Rosalki procedure at 30°C,[14] returned close to the normal range. Cumulative CK appearance was calculated by our previously described modification[15] of the method of Shell and Sobel,[1] and the peak level of CK activity was also noted for each patient.

Left ventriculography and selective coronary arteriography were offered to patients at one month after admission to hospital as part of a wider study of prognosis and the place of coronary surgery after a first infarction. Treadmill stress testing was performed routinely before angiography.

Left ventriculography and selective coronary arteriography were performed by the Judkins procedure,[16] and all left ventriculograms were recorded biplane on 35 mm cine film. The projections used were 35° right anterior oblique (RAO) and 25 to 35° hemiaxial 55° left anterior oblique (LAO). Two methods of estimating infarct size from the cine studies were used, each method being used independently by two radiologists (JS and PB). For the first, termed the "contractility" method, the left ventricle was arbitrarily divided into nine segments (Fig. 1). Contractility of each segment was assessed subjectively and given a "score" as normal (no points), hypokinetic (one point), akinetic (two points), or dyskinetic (three points). As the septum contains about half the left ventricular muscle,[17] yet is profiled in only two of the nine segments, the septal segments were given a multiplication factor of three. Theoretical maximum score (given the impossible situation of all segments being dyskinetic) would be 39. Fig. 2 shows the score for a patient who had akinesia of the anterolateral and apical segments, dyskinesia of the apical septal segment, and normal contractility in the remainder of the profiled segments.

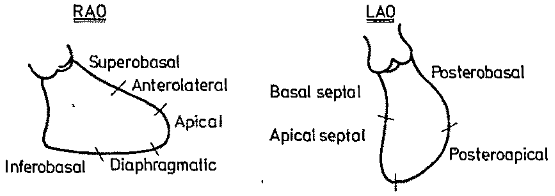


Fig. 1 *Left ventricular segments. "Contractility" method. The diagram on the left shows the five segments in a 35° right anterior oblique projection (RAO), and the diagram on the right shows the four segments in a 55° left anterior oblique projection with a 30° cranial axial tilt (LAO).*

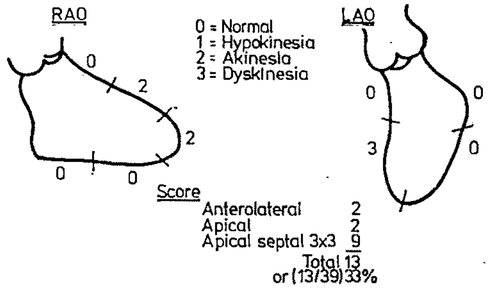


Fig. 2 *Angiocardiographic score—"contractility" method. This is an example of the calculation of the score with this method in a patient with akinesia of the anterolateral and apical segments and dyskinesia of the apical septum.*

The second radiological method for estimation of infarct size was termed the "muscle loss" method. This method was based on the contractile behaviour of the myocardium assessed not only by the appearance of the cavity margins in the biplane ventriculograms, but also by observing the motion of arteries in the septum and on the free wall in the coronary arteriograms. In addition, allowance was made for wall thinning and loss of trabeculation where this could be identified. This method evolved from the style of coronary arteriographic reporting used at Green Lane Hospital[18] where the left ventricular myocardium is divided into defined regions and scored according to the estimated

Table 1 *"Muscle loss" method; multiplication factors for severity*

Angiographic interpretation	*Severity*
Normal	0
Hypokinetic	1
Akinetic without muscle loss	2
Akinetic or dyskinetic with partial muscle loss*	3
Akinetic or dyskinetic with total muscle loss†	4

* Partial wall thinning with some trabeculation visible.
† Thin scar with total loss of trabeculations.

Table 2 *"Muscle loss" assessment of patient with inferior infarction*

*Region**	*Units*	*Severity*	*Score*
Anterior septum	5	0	0
Posterior septum	2	2	4
Diagonal	2	0	0
Obtuse margin	2 1	1 0	2
Inferior LV wall	3	3	9
Total	15	—	15 (25%)†

* See Brandt *et al.*[18].
† Expressed as a percentage of theoretical maximal score 60 (multiplication factor of 4 for 15 myocardial units).

amount of myocardium affected as well as the severity of arterial obstructions. For the estimation of infarct size the severity of observed arterial narrowings was ignored, but the left ventricular myocardium was considered in terms of 15 myocardial units, seven in the septum (divided into anterior and posterior septal regions), two in the diagonal area, and three each on the obtuse margin and inferior surfaces. A subjective estimation of contractile state of each anatomical zone was made using all the information available in the cine studies and using a severity multiplication factor as in Table 1. A complete "muscle loss" assessment in shown in Table 2.

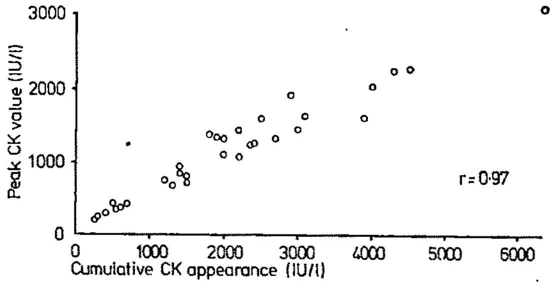


Fig. 3 *Comparison of infarct size assessed by peak CK value and cumulative CK appearance. A strong correlation is shown (r=0·97).*

Table 3 *Comparability of ventriculographic assessments*

Subject for comparison		*Correlation coefficient (r)*
Two ventriculographic methods ("contractility", "muscle loss")	JS	0·91
	PB	0·89
Assessment of two radiologists (JS, PB)	"Contractility" method	0·85
	"Muscle loss" method	0·88

Results

Fig. 3 depicts the very close correlation (r=0·97) between the two enzymic indices. Table 3 shows the slightly weaker correlations (r=0·85 to 0·91) between the two angiographic methods (contractility and muscle loss) in the hands of the same radiologist, and the assessments of the two radiologists (JS and PB), using the same method. An example of this is shown in Fig. 4. Table 4 compares the enzymic with the ventriculographic indices and shows correlation coefficients for all infarcts ranging from r=0·53 to r=0·72. An example of the weaker correlation between enzymic and ventriculographic methods appears in Fig. 5.

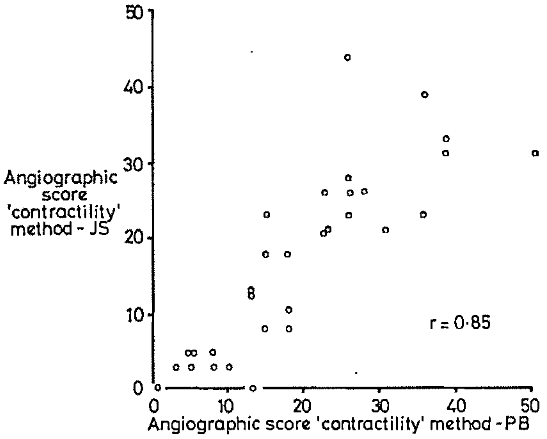


Fig. 4 *Comparison of the two radiologists' angiocardiographic assessments of myocardial damage using the "contractility" method.*

Correlations between enzymic and ventriculographic indices for patients with anterior infarcts (r values ranging from 0·68 to 0·84) were better than those for inferior infarcts (r values from 0·51 to 0·71). There was also a tendency with inferior infarction for relatively more enzyme appearance for a given degree of left ventricular impairment. This tendency did not attain statistical significance, but was evident in all the enzymic/ventriculographic correlations (Fig. 5). Right ventricular infarction was considered likely in four patients with inferior myocardial infarction, who had occlusions of the right coronary artery proximal to all right ventricular branches. Supportive clinical features (right ventricular failure inappropriately severe for the degree of left ventricular failure) were seen in two of these patients. Exclusion of the four patients slightly improved the correlations for inferior infarcts (r values 0·62 to 0·77). In addition, right ventricular infarction may have occurred in other patients with inferior infarction and more distal lesions of the right coronary artery, but this could not be judged with any degree of accuracy.

Table 4 *Comparison of enzymic and ventriculographic estimations of myocardial infarct size (correlation coefficients)*

		"Contractility" method		*"Muscle loss" method*	
		JS	*PB*	*JS*	*PB*
All infarcts	Integral CK	0·68	0·53	0·71	0·64
	Peak CK	0·70	0·55	0·72	0·62
Anterior infarcts	Integral CK	0·76	0·75	0·76	0·72
	Peak CK	0·84	0·75	0·83	0·68
Inferior infarcts	Integral CK	0·67	0·53	0·71	0·66
	Peak CK	0·64	0·51	0·68	0·63

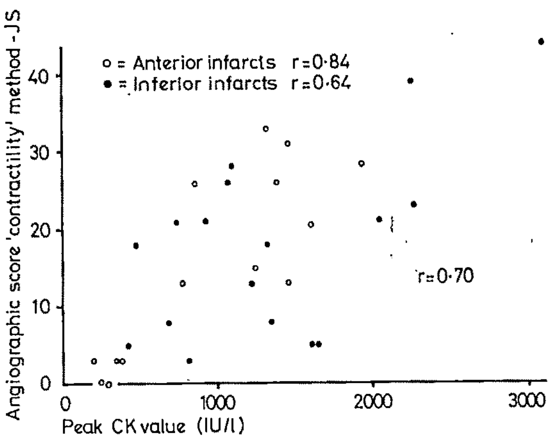


Fig. 5 *Comparison of myocardial infarct size assessed by peak CK value and angiocardiography.*

Three patients with ischaemic myocardium evidenced by angina on stress testing and five who were on beta-adrenergic blocking drugs at the time of angiography did not appear to have a different ventriculographic "score" relative to CK, and their exclusion from the series would not have significantly affected the relations.

Discussion

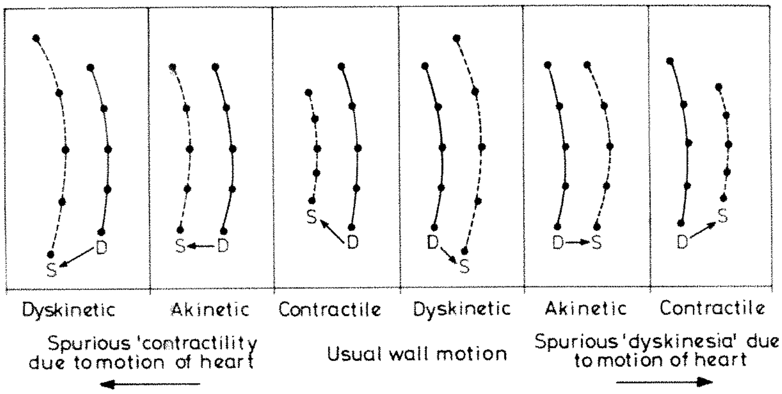
A major problem in the evaluation of therapeutic interventions in myocardial infarction is the difficulty in assessing accurately their effects on myocardial infarct size. Of the methods which are available, analysis of serum CK is a widely used method of assessing myocardial damage.[2 5 6] CK appearance in the serum bears a close relation to myocardial CK depletion[9 10] which itself has been shown in experimental infarction to correlate well with both myocardial blood flow reduction,[19] and histological infarct size.[10 20] A good correlation between myocardial damage measured enzymatically and that assessed clinically[15] and at necropsy[7] has subsequently been reported, while a recent study[8] comparing cumulative cardiospecific CK MB release and two ventriculographic indices of myocardial damage (ejection fraction, and "percentage abnormally contracting segment") has added support to these observations.

The current methods and assumptions in the calculation of CK appearance, however, have recently been questioned on two major grounds. First, the assumed mono-experimental decay rate and identity of the constant (K_D) required for the calculation of integral CK has been challenged theoretically[12] and experimentally.[21] Secondly, in demonstrating in experimental animals that the serum entry ratio may vary with infarct size, Cairns and colleagues have raised the possibility that large infarcts may be underestimated relative to smaller ones.[22]

Our study aimed to provide information on these two issues by comparing the extent of enzyme appearance with the size of the myocardial scar as seen by ventriculography one month later. We have compared angiocardiographic assessments of myocardial damage both with cumulative CK release (which depends on estimates of the rate of removal of CK from the serum, K_D) and the peak CK value which does not require any such estimate. In addition, as our study contains infarcts of a wide range of severity, the variability of CK release relative to angiocardiographic infarct size can be examined.

Correlation between the two enzymic indices (peak CK and integral CK) was very close ($r = 0{\cdot}97$). This is at first sight surprising, because integral CK varies directly with K_D which itself varies widely from patient to patient. A mean value for K_D calculated from previously reported groups of patients had a standard deviation on one-third to one-half of the mean value.[1 15] In the present group ($n = 32$), the mean value for K_D was 0·00090 ±0·00021 SD) min^{-1} so that the standard deviation was approximately 23 per cent of the mean value. Inspection of Fig. 2 shows that a prediction of integral CK from any value for peak CK would have a likely error (±2 SD about the predicted value) of less than 50 per cent. Thus the departure from a perfect correlation between peak CK and integral CK is fully accounted for by the range of K_D; curves of CK appearance in the serum after infarction in other words vary only by their peak values and the exponential slopes of their decay rates from which K_D is calculated. This is not surprising since it is know that CK appearance curves from uncomplicated infarcts have a stereotyped log-normal pattern:[23] The close correlation of peak CK with integral CK suggests that peak CK could be used as a more convenient index of infarct size than the more laborious integral method which entails four-hourly blood sampling for 72 hours or longer for calculation of K_D. In two therapeutic trials of propranolol[6 24] we have found comparisons of peak CK values between treated and control patients to give essentially similar information as comparison of the integrals. Moreover, Armstrong *et al.*[25] have argued on theoretical grounds that peak CK levels are closely related to total CK appearance.

Our radiological technique included biplane films in right anterior oblique and left anterior oblique with cranial axial angulation as these two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Contractile
Spurious 'contractility due to motion of heart
Usual wall motion
Spurious 'dyskinesia' due to motion of heart

Fig. 6 *Diagrammatic representation of pitfalls in the assessment of the contractile state of the ventricular wall by superimposition of diastolic and systolic outlines using external frames of reference. In each diagram the same portion of the ventricular cavity margin is represented in isolation, showing change of position and dimension in diastole (D, continuous line) and systole (S, interrupted line). The diagrammatic individual adjacent portions are separated by dots to emphasise change in dimension. In the centre are the usual appearances of contractility and dyskinesia without interference by motion of the heart as a whole. To each side are examples of possible confusion caused by cardiac motion. The contractile state must be assessed independently of motion.*

projections allow visualisation of all segments of myocardium with least foreshortening of the long axis of the left ventricle. As the septal profile represents nearly half the ventricular muscle[17] this has been taken into account in calculating the "contractility" score.

The analysis of the contractile state of the left ventricular myocardium in our study was done by subjective observation which should allow an experienced analyst to distinguish between changes caused by cardiac motion and variations in the intrinsic contractile behaviour of the region observed. Such subjective analysis must be based on comparison of the relative behaviour of small adjacent components of the profiled area under consideration (Fig. 6). Subjective analysis is frequently difficult and likely to be less reproducible than objective measurements.[26] It is therefore not surprising that the interobserver correlations were below 0·9. This is not to say that an objective method necessarily is more accurate in categorising the contractile state of the myocardium. Objective methods using internal frames of reference[26–28] may be useful but we have not yet attempted to apply them to the assessment of infarct size.

The method described by Rogers *et al.*[8] uses an external frame of reference and was applied originally to serial large film studies. It is based on superimposition of systolic and diastolic outlines without allowing for the possibility that a non-contractile region can be moved centrally by adjacent contractile regions or that unusual cardiac motion can cause superimposition or even paradoxical overlap of a contractile region (Fig. 6). It should be noted that the definitions of "akinesia", "dyskinesia", and "hypokinesia" used by Rogers *et al.*[8] did not relate directly to the contractile behaviour of the muscle, and their conclusions regarding lack of correlation between "hypokinesia" and infarction do not apply to more accurate assessments of the contractile state. Thus nine (28%) of our patients with small infarcts showed only hypokinesia by our method. In the left anterior oblique projection the forward systolic motion of the aortic root and the base of the heart gave an "abnormally contracting segment"[8] by superimposition of systolic and diastolic outlines using external frames of reference in 30 patients (94%) (Fig. 7). In only six cases was this considered to be associated with infarction in the basal septum. In the others it was a result of normal forward motion of the base of the heart. Making allowance for this region, 14 (44%) of our patients would have shown no abnormally contracting segment by superimposition of systolic on diastolic outlines using an external frame of reference (Fig. 7).

This evaluation of myocardial damage by left ventriculography makes the basic assumption that the severity of infarction in a given area is reflected by the severity of subsequent contractile disorder. A small subendocardial infarct should show only slight hypokinesia or normal appearances, more severe infarction should result in more severe hypokinesia or akinesia, depending on the propor-

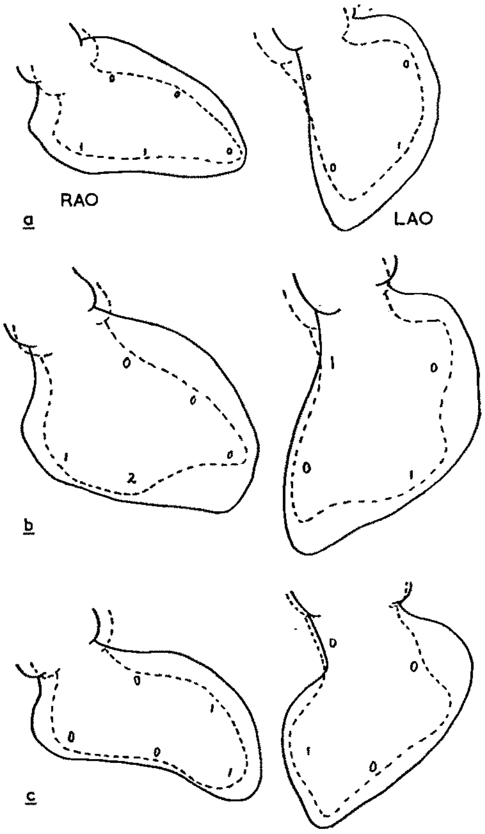

Fig. 7 *Superimposed end-diastolic (continuous lines) and end-systolic (interrupted lines) left ventricular outlines in right anterior oblique (RAO) and left anterior oblique with cranial axial angulation (LAO) projections in three patients. External frame of reference determines the positions of the tracings as the* x-*ray beam and patient were not moving and there was no respiratory motion, the frames being traced on to the same piece of paper in the analysing projector. These examples were selected to illustrate some of the difficulties in applying this method to the assessment of contractility. All three cases in LAO show an "abnormally contracting segment" of the basal septal region due to cardiac motion. Only in* (b) *was this associated with hypokinesia. In* (a) *the infarcted area was readily recognised subjectively but would have escaped detection by this method. In* (b) *where a larger infarct associated with an akinetic area inferiorly caused a severe irregularity of contour, cardiac motion, nevertheless, allowed the whole systolic contour to fall within the diastolic contour. In* (c) *the hypokinetic anterolateral contour in RAO is made by cardiac motion to appear more contractile than the normal inferior surface. Numbers indicate the subjective assessment of the contour margins as in Fig. 2.*

tion of the contractile muscle and scar tissue, and dyskinesia should indicate severe infarction with thinning of the ventricular wall. These assumptions are not always correct as the contractile behaviour can be modified by ischaemia or drugs.[27] Moreover, though good wall motion means normal myocardium, normal myocardium does not necessarily mean good wall motion.[28] Though our patients taking beta-blocking drugs and those who had angina on exercise did not show a different correlation from the other patients, it is possible that the ventriculographic appearances overestimated myocardial necrosis to a variable degree by showing contraction abnormalities in normal myocardium adjacent to the infarct or in viable myocardium perfused by a stenotic vessel.[29] Other sources of error include (in the case of left ventriculography) technical failure to visualise all left ventricular myocardial segments, the difficulty of analysing the various contractile states, and inability to assess right ventricular abnormalities which are common in inferior infarction.[30] Our results suggest that associated right ventricular infarction in some cases of inferior myocardial infarction could explain both their poorer correlation with angiographic indices and their tendency for higher enzyme levels for a given degree of left ventricular impairment.

Sources of error in the enzyme measurements include biological variation in the CK content of normal myocardium and its depletion by infarction,[11] contribution of non-cardiac CK to total CK appearance, and variations in serum entry ratio probably caused by varying degrees of CK degradation locally within the infarct.[22] For reasons discussed earlier, it is possible that variability of K_D may be of somewhat lesser importance.

Considering all of these possible sources of error, it is not surprising that the correlations we have shown between enzymic and cineangiocardiographic indices are less than ideal, varying considerably with the method used for quantification of the angiocardiograms as well as with the differing subjective impressions of different radiologists who interpret them. Moreover, the invasive nature of ventriculography and its restriction to patients without previous myocardial damage makes it unsuitable for routine use. At the present time there is no "gold standard" for the measurement of infarct size, and its severity is perhaps best assessed by the combined use of clinical, enzymic, and electrocardiographic indices. To these methods can be added others such as ventriculography, nuclear imaging, or echocardiography, where these are specifically indicated. Of laboratory-based methods which are available, the enzymic method is the most reliable. Peak CK activity based on four-hourly blood sampling may provide sufficient information as an index of myocardial infarct size for an end-point for the clinical trial of therapeutic agents which are designed to reduce it.

We are grateful to Dr E A Harris for assistance with statistical analysis.

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Treatment of acute myocardial infarction with propranolol

*Further studies on enzyme appearance and subsequent left ventricular function in treated and control patients with developing infarcts**

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SUMMARY The effect of propranolol 0·1 mg/kg intravenously followed by 320 mg in divided doses given over 27 hours orally was further evaluated in a randomised trial involving 62 patients up to 65 years of age who were seen within four hours of onset of uncomplicated myocardial infarction. Thirty-three patients were given propranolol and 29 served as controls. Two indices of infarct size were used: (a) total creatine kinase appearance and peak activity levels measured during the acute stage of infarction, and (b) subjective analysis of biplane left ventriculograms performed one month later in a subgroup of these patients. Total enzyme appearance was reduced by 25 per cent and peak levels were reduced by 23 per cent in treated patients compared with controls. The subgroup subsequently studied by angiocardiography did not show the reduction in enzyme levels shown by the whole group; likewise, quantitative subjective analysis of the left ventriculograms did not show any significant difference between the two groups. Though it could not be confirmed by this radiological method that reduction in enzyme appearance by beta adrenoceptor blockade was associated with restriction in infarct size, this seems the most likely cause for the lower enzyme levels. The safety of intravenous beta blockade when used in carefully selected patients suggests that large-scale clinical trials can be recommended in which measurements of infarct size as well as morbidity and mortality can be used as end-points.

We have previously shown that patients treated with intravenous and oral propranolol starting within four hours of the onset of uncomplicated myocardial infarction have lower serum creatine kinase (CK) levels than control patients.[1] We also found subsequently that patients with 'threatened' infarction given intravenous and oral propranolol within four hours of the onset of pain had fewer completed infarcts assessed by standard electrocardiogram than did control patients.[2] The present study aimed to carry these trials further by investigation of a new group of treated and control patients at one month after infarction by exercise testing biplane cineangiocardiography as well as with enzyme measurements during the acute phase. In this way we hoped first, to check again that enzyme levels were reduced in treated patients if propranolol was given within four hours of the onset; second, to see if the reduction in enzyme levels (if confirmed) was associated with improved left ventricular contractility assessed by biplane angiocardiograms; third, to establish whether treated patients had greater evidence of myocardial ischaemia assessed by exercise testing one month after treatment than did the control patients. Salvage of ischaemic myocardium from infarction by propranolol might have rendered the myocardium chronically ischaemic, and this might be detected during exercise.

Patients and methods

As in our previous study,[1] we aimed to select patients who were in the early stages of uncompli-

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*This work was supported by the Medical Research Council and the National Heart Foundation of New Zealand.

Received for publication 19 October 1979

cated transmural infarction as evidenced by (a) typical history of prolonged chest pain with onset less than four hours previously and (b) ST segment elevation in the electrocardiogram of greater than 2 mm in the anterior chest leads, greater than 1 mm in leads II, III, and aVF, or pathological Q waves. Patients had to be no more than 65 years of age, with no history of bronchial asthma, systolic blood pressure above 100 mmHg, heart rate greater than 60/minute, and without breathlessness or basal râles. Patients who had had DC cardioversion were excluded. An anteroposterior chest *x*-ray film taken immediately after admission to the coronary care unit was examined before entry to the trial and patients with *x*-ray evidence of interstitial oedema or pulmonary oedema were rejected though cases showing pulmonary venous congestion without oedema were accepted. Immediately on entry to the trial patients were randomised by the envelope method for treatment with propranolol or no specific treatment. Treated patients were immediately given propranolol 0·1 mg/kg intravenously over 10 minutes followed by 320 mg orally over the next 27 hours. This was given in divided doses of 40 mg at one, three, seven, 11, 15, 19, 23, and 27 hours after entry to the trial. Before each oral dose the patients were assessed by the nurses; if the systolic blood pressure was below 100 mmHg or the heart rate below 50/minute the next dose was omitted and the patient was assessed again in the same way before the next dose was due. No injections were given intramuscularly during the period of the trial. Lignocaine was used as necessary in both treated and control patients for the control of ventricular arrhythmias and in a few cases intravenous or oral frusemide was given for left ventricular failure. In most patients, however, no other specific treatment was given during the period of the trial.

Blood was taken every four hours from an intravenous catheter (Intracath) inserted percutaneously into an antecubital vein. Blood was used for measurement of creatine kinase activity by Rosalki's method[3] using a Bausch and Lomb system 400. Serum propranolol was measured by a fluorimetric method.[4] Specimens for measurement of CK activity were taken for approximately 72 hours or until the enzyme activity had peaked and returned to near normal levels. For calculation of total CK appearance we used our modification[5] of the method of Sobel *et al.*[6] This modification is based on calculation of an individualised decay rate (KD) for enzyme activity which is used for calculation of the total enzyme appearance. As the peak activity measured four hourly correlates closely with the calculated total enzyme appearance[7] we used both the peak CK levels as well as the calculated total appearance as indices of infarct size.

Dosage of propranolol was discontinued at 27 hours and patients were mobilised and discharged in most cases after seven to 14 days in hospital. As part of another study of long-term prognosis in male patients under 60 years of age surviving a first myocardial infarct,[8] some patients were readmitted for two days for exercise testing and angiocardiography at one month after the infarct. Only male patients up to 60 years of age who had been admitted to one of the two participating hospitals (GLH) during the acute phase were considered for angiocardiography. Thus the subgroup selected for cardiac investigations was smaller than the original group of patients, 13 of 29 control patients and 15 of 33 treated cases being studied angiocardiographically.

At readmission to hospital one month after the infarct patients were clinically reassessed and then exercised on a treadmill at 2½ miles per hour for three minutes on the flat and then three, three, and six minutes at a gradient of 5, 10, and 15 per cent, successively. Exercise was stopped if significant angina or dyspnoea developed and a 12 lead electrocardiogram was recorded immediately after exercise. Left ventriculography and coronary angiography were done using the Judkins technique and recording the left ventriculogram simultaneously in 35° right anterior oblique and 25 to 35° hemiaxial 55° left anterior oblique projections. Left ventricular contractility was assessed by subjective segmental analysis of wall motion[7] both by using the segmental contractility of the cardiac silhouette in the two projections of the left ventriculogram (contractility method) and also the movement of the vessels in the coronary arteriograms together with the thickness of the left ventricular wall where this could be identified (muscle loss method).

Results

Sixty-two patients entered the trial which was in progress between March 1977 and March 1979; of these, 33 were randomly allocated to the treatment group and 29 to the control group. Details of age, sex, and position of infarct are given in Table 1, and mortality and morbidity data in Table 2. Selection of patients who were free from overt cardiac failure, not hypotensive, and had not had cardiac arrest ensured that a relatively low risk group of patients was studied. Only one of the 62 patients died in hospital; he was in the treated group but was given only three doses of propranolol because of the development of mild hypotension.

Table 1 *Patients admitted to trial*

	Treated	*Control*
Total cases	33	29
Age in years (mean and range)	51 (31–64)	51 (37–65)
Sex	31 M 2 F	27 M 2 F
Position of infarct*	17A, 13I, 3S	14A, 14I, 1 AI

*A, anterior; I, inferior; AI, anterior and inferior; S, subendocardial (see text).

Table 2 *Complications in treated and control patients*

	Treated *(n=33)*	*Control* *(n=29)*
Death in hospital	1	0
Ventricular fibrillation	1	1
Cardiogenic shock	1	1
Left ventricular failure	3	8
Atrioventricular block 2° or greater	0	2

His clinical condition remained satisfactory until 34 hours after the onset when he died suddenly after a further short episode of chest pain and without any change in cardiac rhythm. The circumstances of death suggested cardiac rupture, but permission for necropsy was refused. One treated and one control patient had ventricular fibrillation and both were successfully resuscitated; blood specimens for enzyme activity were discarded after cardioversion, but in the treated patient sufficient information was available before ventricular fibrillation for calculation of the enzyme appearance. Cardiac failure developed in 11 patients but was relatively mild in all cases and responded to treatment with frusemide. Sinus bradycardia (not shown in Table 2) was more common in patients given propranolol. This did not usually require treatment, but in a few cases responded quickly to atropine 0·3 mg intravenously.

The peak measured CK activity levels and calculated total enzyme appearance for treated and control patients are shown in Fig. 1 and 2. Though the range was wide, peak levels in the treated patients were 23 per cent lower on average than in the controls, and this difference was significant ($t=2{\cdot}27$, $p<0{\cdot}05$). Similarly, the calculated total CK appearance was 25 per cent lower in the treated patients than in the controls ($t=2{\cdot}21$, $p<0{\cdot}05$). For the subgroup of patients who were subsequently investigated, however, the differences were less and were not statistically significant (treated cases 10% lower for peak enzyme levels; $t=0{\cdot}65$, $p>0{\cdot}5$, and 13% lower for total enzyme appearance; $t=0{\cdot}79$, $p>0{\cdot}5$). Serum degradation rate (KD) of CK activity, calculated from the rapid phase of decline in enzyme levels, was not altered by propranolol (KD in treated patients=0·00086 ±0·00019/min, and in controls=0·00087±0·00019/min).

Examination of the electrocardiogram on which entry to the trial was based showed that in 12 treated and in 11 control patients pathological Q waves were not yet present at entry so that ST segment elevation (in addition to the history) was the sole criterion for inclusion in the trial. All 11 control cases and nine of the 12 treated patients finally developed pathological Q waves. The other three treated patients all developed T wave changes without Q waves and were considered to have had subendocardial infarcts.

The results of clinical evaluation and exercise testing one month after the infarct are shown in Table 3. The incidence of ischaemic pain between

Table 3 *Clinical evaluation at one month after infarction*

	Treated *(n=15)*	*Control* *(n=12)*
Further ischaemic pain	7	6
Angina on exercise testing	2	4
*Ischaemic ST changes after exercise	1	3

*Flat or downsloping ST depression of 1 mm or greater.

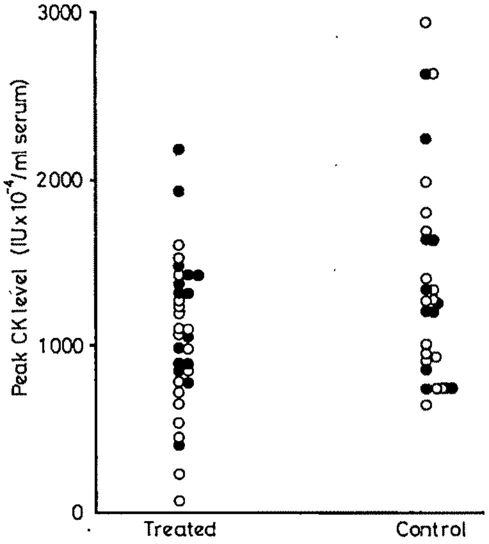

Fig. 1 *Peak CK activity levels in treated and control patients. Levels were 23 per cent in the whole group of treated patients ($p<0{\cdot}05$), but were not significantly lower in the subgroup* (closed circles) *who were subsequently investigated by left ventriculography. Figures were not available for one control patient who had ventricular fibrillation.*

discharge from hospital and readmission for the exercise test, the incidence of angina during the test and of ischaemic electrocardiographic abnormalities afterwards, were all similar in the treated patients and in the controls. Only two of these patients (one treated and one control) were taking beta blockers at the time of exercise testing.

The angiographic score for left ventricular function calculated by the 'muscle loss' method[7] is plotted against the calculated total CK appearance for treated and control patients in Fig. 3. Similar results were obtained assessing peak enzyme levels and the angiographic score by the 'contractility' method (data not shown). Unexpectedly, the mean figure for the scores shown in Fig. 3 was 23 per cent higher for the treated patients than for the controls, but this difference was not significant ($t=1.16$, $p>0.3$). The correlation coefficient for all cases (treated and control) shown in Fig. 3 between the contractility score and the integrated enzyme appearance was $r=0.54$. Inspection of Fig. 3 shows a possible tendency towards a greater scatter of data for the treated patients when compared with the controls. The possibility that the relation between ventriculographic score and enzyme appearance had been altered by propranolol was tested in two ways (a) by comparing the correlation coefficients of control with treated cases; and (b) by comparing the slopes of the regression lines describing the relation for the two groups separately. Neither comparison showed any significant difference between the two groups, and the same negative result was obtained when the ventriculographic score was calculated by the 'contractility' method and when the peak measured level of CK rather than the calculated total appearance was used as the enzymic index of infarct size.

Discussion

This study has confirmed our previous findings that peak CK levels and total CK appearance are reduced in patients with developing transmural infarction who are given intravenous and oral propranolol within four hours of the onset. However, it has failed to show a corresponding improvement in left ventricular function resulting from the intervention when this was assessed by biplane cineangiocardiograms one month later. Unfortunately, the subgroup selected for angiography did not show the significant reduction in enzyme levels shown by the larger group so that the hypothesis that a reduction in enzyme levels during the acute phase of infarction is associated with better left ventricular function afterwards could not be tested.

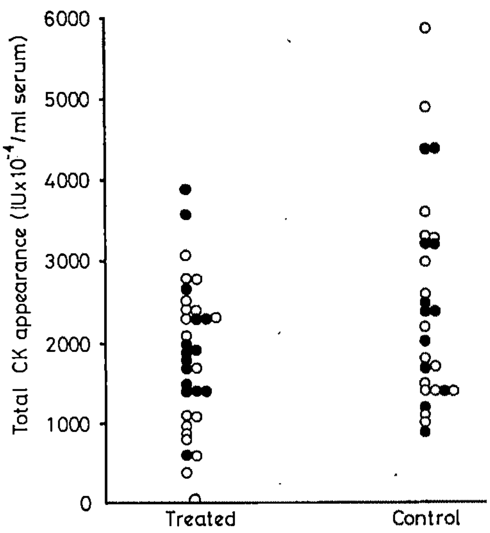

Fig. 2 *Total calculated CK appearance in treated and control patients. Total appearance was 25 per cent lower ($p<0.05$) in the whole group of treated patients but was insignificantly lower in the subgroup* (closed circles) *who were subsequently investigated by left ventriculography.*

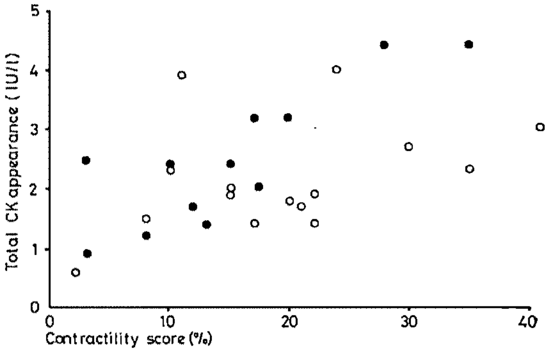

Fig. 3 *Relation between segmental contractility score subjectively assessed from biplane left ventriculograms and total enzyme appearance in control* (closed circles) *and treated* (open circles) *patients. Correlation coefficient (r) for all cases = 0·54. Though the relation between enzyme appearance and contractility score appears to be less close for the treated patients than for the controls, and in some treated patients there appears to be excessive loss in contractility for the amount of enzyme appearance, neither tendency was statistically significant. Use of another index for enzyme appearance (peak levels) and an alternative method for assessment of contractility from the angiocardiograms similarly did not show any difference between treated and control cases.*

There are a number of possibilities which might account for lower enzyme levels with propranolol. First, reduction in collateral blood flow by the beta blocker might reduce enzyme wash-out, causing more enzyme to be degraded locally within the infarct and less to appear in the circulation. Thus a reduction in serum enzyme levels might be seen without any corresponding change in infarct size. Cairns *et al.*[9] have shown experimentally that the serum entry ratio (proportion of CK released into the circulation) is lower in large than in small infarcts, and this is presumably caused by lower collateral blood flow at the centres of large infarcts. Though some workers have shown a reduction in infarct blood flow in anaesthetised animals pretreated with propranolol,[10] we found no change in collateral blood flow,[11] and studies on conscious dogs (which would presumably be more comparable with patients) showed that collateral flow was increased rather than decreased.[12 13] Moreover, animal experiments have shown higher tissue CK levels (compared with controls) at the centres of infarcts in dogs pretreated with propranolol.[14 15] If the effect of propranolol is to increase local degradation of enzyme activity the tissue levels should not be higher in treated animals than in controls.

A second possible reason for lower serum enzyme levels in patients is that propranolol increases the degradation rate of CK in the bloodstream. Though some experimental work suggests that such an effect may operate[16] the measured degradation rate of enzyme activity (KD) in the present study and also in our previous trial[1] was similar in treated and control patients. It is true that dosage with propranolol had stopped while KD was being measured, but blood levels were still in the therapeutic range and haemodynamic effects of beta blockade were still present in many of the treated patients during the period of rapid decline in enzyme activity. Thus it seems unlikely that serum enzyme degradation rates were increased by propranolol.

The most likely explanation for the lower serum levels is that myocardial viability is preserved by the oxygen-sparing action of propranolol, so that fewer myocardial cells became necrotic and less enzyme activity leaked out. In support of this idea is our previous finding[2] suggesting that the electrocardiographic abnormalities of 'threatened' infarction can in some cases be prevented by intravenous propranolol. In this context it is of interest that three out of 12 patients in the present trial who had ST segment elevation but no pathological Q wave in the 12 lead electrocardiogram at entry did not finally develop pathological Q waves. In our first study[1] there were also three patients (out of 10 with no Q waves at entry) who were treated with propranolol within four hours of the onset and did not finally develop Q waves. Combining the results of both trials, six out of 22 treated patients and zero out of 19 control patients who had no Q waves at entry did not finally develop them. This event is not statistically significant ($\chi^2=2\cdot94$, $p<0\cdot10>0\cdot05$). However, in conjunction with the other findings, it does seem to support the possibility that beta blockade protects infarcting myocardium when it is given early.

Reduction of myocardial necrosis by beta blockers, if it occurs, may or may not be beneficial for patients. If some myocardium remains chronically ischaemic rather than infarcted it might cause angina after the infarct or else act as a focus for the development of re-entrant arrhythmias. Exercise testing at one month in the present small group of patients did not suggest that treated patients had more ischaemia, but this point obviously needs to be reassessed in a larger series. Our patient numbers are not sufficient to evaluate the effect of treatment on the subsequent incidence of arrhythmias and sudden death and this, too, would require a large and probably multicentre trial. The present study has failed to show any improvement in left ventricular function in the treated patients compared with the controls. This may be because of the small numbers and the fact that the patients in whom left ventricular function was assessed were not truly representative of the treated and control groups. Even if myocardium were preserved, however, this might not result in improved ventricular function. It is known that though dead muscle results in loss of contractility angiographically, loss of contractility does not necessarily mean dead muscle.[17] Thus, infarcted myocardium might be preserved but still might not show normal contraction subsequently, particularly if it remained chronically ischaemic.

Demonstrations of the safety of intravenous propranolol in the present and previous trials[1 2 18] suggest that large-scale clinical trials can now be recommended if entry is restricted to patients who are not hypotensive and do not show overt cardiac failure. Indeed, some preliminary studies we have made using haemodynamic monitoring in patients with early failure suggest that beta blockade can be given cautiously and in conjunction with a diuretic to patients who are breathless with early interstitial pulmonary oedema. Thus, there seems little risk of exacerbation of cardiac failure if patients have a blood pressure of more than 100 mmHg and do not have breathlessness or basal râles before administration of the beta blocker. Though beta blockade should be used cautiously in the presence of bradycardia, we have found that severe bradycardia responds readily to atropine. Thus in our experience beta blockers appear to be safer, particularly for prehospital use, than other oxygen-sparing drugs such as glyceryl trinitrate which reduce the afterload to ventricular contraction but may cause a disastrous fall in blood pressure if the dose is not strictly monitored.

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Br Heart J 1980; **43**: 623–8

Evaluation of ejection murmurs by pulsed Doppler echocardiography*

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SUMMARY A common problem is a soft basal ejection murmur in an asymptomatic child with a normal electrocardiogram and chest *x*-ray films. If the diagnosis is aortic stenosis, there is a need for prophylaxis for subacute bacterial endocarditis and concern about development of calcific aortic stenosis. In 40 consecutive children referred for this differential diagnosis, aortic stenosis was diagnosed in 30, based on an ejection murmur at the second right interspace (not necessarily louder than at the second left), which transmitted well to the neck, accompanied by a normal second heart sound. Pulsed Doppler echocardiography confirmed turbulence at the aortic valve in 26. In the 10 children diagnosed clinically as having an innocent murmur, three had evidence on pulsed Doppler echocardiography for an abnormal aortic valve. The conventional echocardiographic findings of an eccentric aortic orifice were present in only 21 of 29 patients with aortic turbulence. Though our current clinical criteria are reasonably specific (87%), they are not as sensitive (70%). Pulsed Doppler echocardiography provides powerful non-invasive assistance for this important differential diagnosis.

Clinically significant aortic stenosis is diagnosed by the presence of a grade 4/6, or louder, rough ejection murmur at the base of the heart, prominent at the second right intercostal space, well transmitted to the suprasternal notch and carotids, and towards the cardiac apex.[1] There may be an ejection click,[2] and audible aortic regurgitation.[3] The additional presence of electrocardiographic (left ventricular hypertrophy) or radiological changes (left ventricular enlargement or post-stenotic dilatation of the ascending aorta), and the presence of a thrill are emphasised by others.[4–6]

A more common—and more difficult—problem is the asymptomatic child with a grade 2–3/6 ejection murmur at the base of the heart with a normal electrocardiogram and chest *x*-ray film. Since over a half of normal children have innocent murmurs, the majority of which are ejection murmurs, the differential diagnosis between aortic origin and pulmonary origin of this murmur is probably the most common cardiological problem that the family practitioner and paediatrician encounter in their practice. Whether this murmur represents an innocent ejection murmur, mild pulmonary stenosis, or mild aortic stenosis will determine whether the patient is at risk for infective endocarditis and progression in later life to early calcific aortic stenosis.[7] Though there are no known preventive measures for calcific aortic stenosis, infective endocarditis is a serious complication with high mortality and morbidity, and prophylaxis is thought to be effective in its prevention. Clearly, the cost and morbidity[8] for invasive studies argue against their application to this huge group of youngsters with the differential diagnosis of innocent murmur versus mild aortic or pulmonary stenosis. The problem then is an absence of objective information to validate the conclusions based only on physical examination, a situation vulnerable to arbitrary definitions.

Non-invasive approaches of validating the diagnosis of the milder forms of aortic stenosis have not been specific enough. Phonocardiography is an established method of timing auscultatory findings, but it cannot establish the intravascular origin of the murmur. Conventional echocardiography greatly enhanced the detection of bicuspid aortic valves; eccentricity of the coapted aortic leaflets in diastole is well accepted,[2] and the absence of high frequency systolic flutter of the aortic leaflets has

* Supported in part by NIH grants.

Received for publication 12 September 1979

been suggested as diagnostic of abnormal aortic valves.[9]

Pulsed Doppler echocardiography is a relatively new technique capable of localising murmurs within the heart and blood vessels.[10] In essence, pulsed Doppler echocardiography is a non-invasive intravascular phonocardiogram, combined with echocardiography. The combination permits the precise localisation of turbulence within the heart and great vessels. Obviously, specific inferences as to the cause of the turbulence require additional clinical information. In the present application, we are concerned with the origin of an ejection murmur, and whether there is abnormal systolic or diastolic turbulence at either semilunar valve. If there was no turbulence for either valve, and the valve orifice was concentric, the ejection murmur could logically be labelled innocent. If turbulence was found at, above, or below the aortic or pulmonary valve, that valve would be established as the site of origin of the murmur. Pulsed Doppler echocardiography was conducted without knowledge of the results of the physical examination. Our purpose was to validate the clinical conclusions based on conventional criteria of the physical diagnosis with the independent data of intracardiac turbulence by pulsed Doppler echocardiography.

Subjects and methods

Forty consecutive children ranging in age from 2 to 15 years with the clinical question of innocent murmur versus mild aortic stenosis were evaluated by physical examination, electrocardiogram, and chest *x*-ray film, by conventional M-mode echocardiography, and by pulsed Doppler echocardiography. The patients were examined by two cardiologists, and the consensus remained unknown to the echocardiographers until the data were tabulated.

A conventional M-mode echocardiogram was performed, examining carefully for valvular abnormalities such as redundant leaflet echoes, abnormal motion, asymmetry, and great vessel size, in addition to the usual echocardiographic indices.

At the conclusion of the conventional M-mode examinations pulsed Doppler echocardiography was performed to evaluate blood flow characteristics in heart chambers and great vessels, from standard praecordial and suprasternal approaches. The technique of pulsed Doppler echocardiography has been reviewed recently.[10] The method combines M-mode echocardiography with a simultaneous measurement of Doppler-shift of the frequency of reflected sound; the Doppler signal is obtained at a controlled depth within the cardiac structures. The sampling site is indicated by a straight line superimposed on the M-mode echocardiogram. The sample volume is relatively small, a tear-drop shaped volume 4 mm in length and 2 mm at its greatest diameter. By moving the sample volume throughout the heart and great vessels, one can sample blood flow characteristics at known sites (Fig. 1). One output from the Doppler instrument* is an audio signal; a smooth audio signal is produced by smooth blood flow, and turbulent blood flow produces a coarse, rough audio signal. Another output of the pulsed Doppler echocardiographic unit is a time-interval histographic spectral record. This graphic method indicates turbulence by an increased spectral bandwidth, presenting as a wide scattering of the dots forming the envelope which outlines the magnitude and direction of blood flow. Fig 2 and 3 show examples of normal and abnormal blood flow records above the aortic valve with pulsed Doppler echocardiography from the suprasternal notch and praecordial approaches, respectively. Fig. 4 shows the normal flow record in the left ventricular outflow tract during systole and diastole.

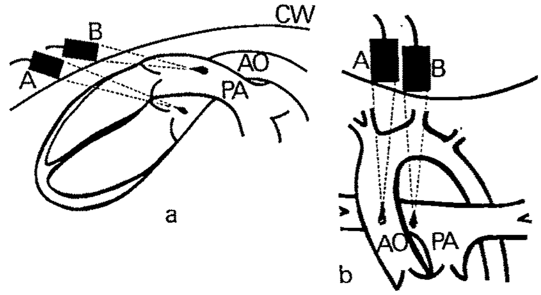

Fig. 1 *Praecordial and suprasternal notch pulsed Doppler echocardiographic examination.* (a) *Praecordial approach. CW, chest wall; AO, ascending aorta; PA, main pulmonary artery; A, transducer position with sample volume (stippled tear drop) in AO; B, transducer position with sample volume in PA.* (b) *The suprasternal notch approach. At transducer position A, sample volume is in AO. At transducer position B, sample volume is in right pulmonary artery.*

The audio output is superior to the graphic method of analysis for detecting subtle degrees of abnormal turbulence, in a manner similar to a trained musical ear detecting the sound of an oboe

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*Advanced Technology Laboratories, Bellevue, Washington, Model 400A or 600A, 5 or 3 mHz.

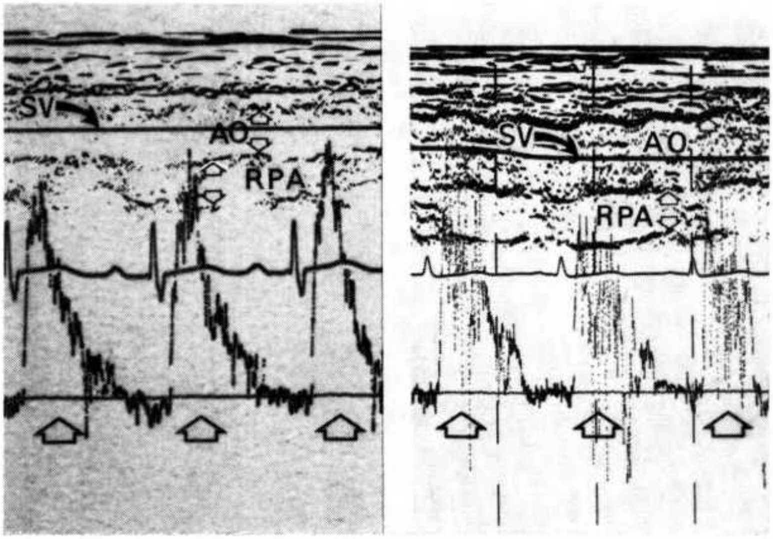
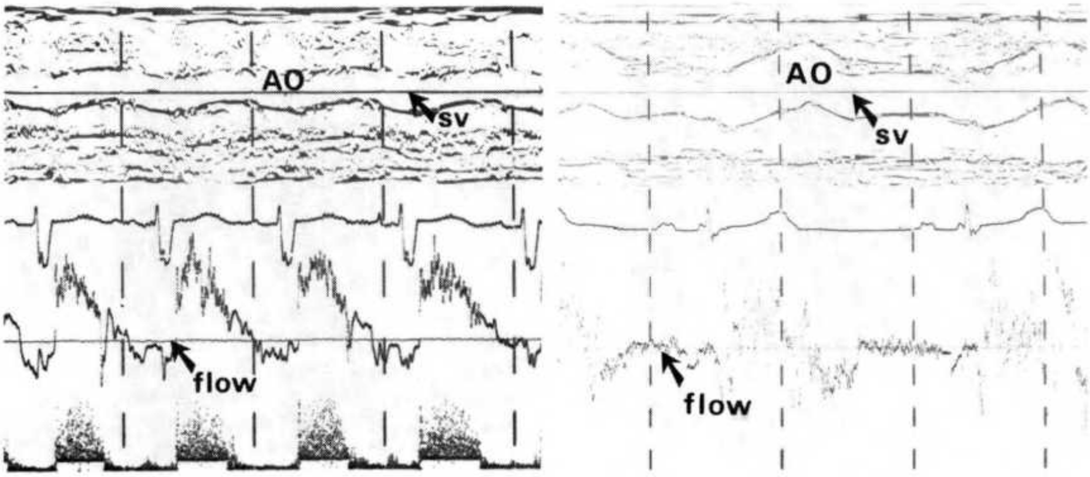


Fig. 2 *Pulsed Doppler echocardiographic flow record from suprasternal notch examination. These two panels show compressed M-mode echocardiographic tracings at the top, and the time interval histogram at the bottom, as recorded from the suprasternal notch approach. AO, aorta; RPA, right pulmonary artery; SV, sample volume.* Left, *the walls of the aorta and right pulmonary artery are indicated by the small arrows, and share a common wall echo. The sample volume position is shown by the location of the line on the M-mode tracing. The graphic recording of the flow record is at the bottom of the panel. The small dots comprising the time-interval histographic record are grouped closely together in a wave form in systole* (large arrows). *This type of flow record is seen when smooth laminar flow is present.* Right, *from another patient the M-mode echocardiographic tracings are compressed at the top showing the aorta, right pulmonary artery, and the location of the sample volume in the aorta, and the graphic recording of the flow record is at the bottom of the panel. The dots of the time interval histogram are very scattered in systole, representing the rough systolic flow* (large arrows). *The dots are not scattered in diastole; the diastolic flow is not rough.*



a b

Fig. 3 *Pulsed Doppler echocardiographic flow record from praecordiol examination. These two panels show compressed M-mode echocardiographic tracings at the top, and the time interval histogram at the bottom as recorded from the praecordial approach. AO, aorta; SV, sample volume; flow, time interval histographic flow record.* (a) *With SV in AO, shows a record of normal flow above the aortic valve. Systolic flow, above the zero reference line (flow) is comprised of closely grouped dots, indicating normal systolic flow. The diastolic interval is also normal. This record of normal systolic flow would correspond to a smooth audio output.* (b) *With SV in AO, shows the flow in a patient with aortic stenosis. The systolic portion of the flow record consists of widely scattered dots, indicative of rough systolic flow. This would correspond to a rough audio output.*

in an orchestra, whereas spectral analysis might be overwhelmed by the entire orchestra. Though abnormal turbulence is not defined numerically for pulsed Doppler echocardiography, a standardised method has been used in our institution for the past two-and-a-half years on over 1000 children. In this study, objectivity was maintained by performing the examination without knowledge of the clinical impression. The presence or absence of turbulence was determined at, above, or below the aortic valve and at, above, or below the pulmonary valve or in the right pulmonary artery.

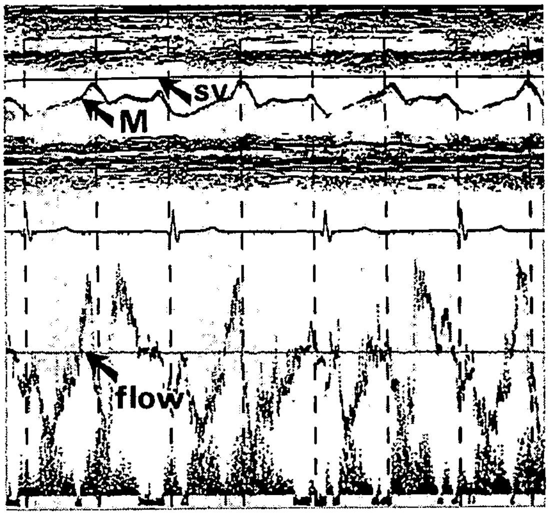


Fig. 4 *Pulsed Doppler echocardiographic record of normal flow in the left ventricular outflow tract. M, mitral valve; SV, sample volume; flow, time interval histographic flow record. The SV has been placed in the left ventricular outflow tract, just anterior to the mitral valve leaflet (M). The flow record is comprised of closely grouped dots, and would correspond to a smooth audio output. As the mitral valve opens, flow proceeds towards the praecordial transducer, corresponding to valve motion. During systole, flow proceeds from the outflow tract toward the aorta, indicated by negative deflection of the flow record during systole. Throughout the cardiac cycle, there is close grouping of dots in the flow record. Such a record of normal flow in the left ventricle could be seen in a patient with normal aortic flow, or in a patient with aortic stenosis. In the normal patient, the aortic flow record would be similar to that shown in Fig. 3a. In a patient with valvar aortic stenosis, the normal left ventricular flow record would change to one similar to Fig. 3b, as SV is moved to aortic valve. The dot scatter, noted as SV is placed at and distal to the aortic valve is indicative of turbulent blood flow arising at the aortic valve.*

Results

On the basis of our clinical findings, we diagnosed aortic stenosis in 30 of the 40 patients (Fig. 5). In all of these children, an ejection murmur was present at the base, prominent in the aortic area, though not necessarily louder than at the pulmonary area, and the murmur was judged to transmit well to the neck. An additional finding that was regarded as evidence of an aortic valve abnormality was a soft diastolic murmur presumed to be of aortic origin. An ejection click was frequently present, but not consistently. The second sound in the pulmonary area was judged to be normal in all.

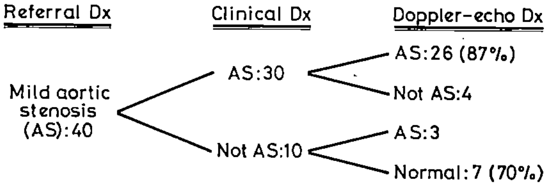


Fig. 5 *The patient distribution based upon clinical evaluation and the diagnoses based upon pulsed Doppler echocardiography evaluation are shown.*

Of the 30 patients diagnosed clinically as having mild aortic stenosis, 26 had one or more M-mode or Doppler criteria of an abnormal aortic valve. Eccentricity of the valve leaflets was diagnosed in 20. Turbulence was detected by pulsed Doppler echocardiography at the aortic valve in all 26, and turbulence in the ascending aorta was found in 24. Mild aortic regurgitation (diastolic turbulence below the aortic valve) was present in 12 subjects. Of the four subjects diagnosed clinically as aortic stenosis but without aortic abnormalities on pulsed Doppler echocardiographic examination, one had Doppler evidence of pulmonary regurgitation (the regurgitant murmur on physical examination had incorrectly been attributed to the aortic valve), one had systolic turbulence only in the main pulmonary artery, and two children had no detectable abnormalities by conventional echocardiogram or pulsed Doppler echocardiography.

In the 10 youngsters who were diagnosed clinically as having an innocent murmur, three had turbulence at the aortic valve and ascending aorta, and one of those had eccentricity of the aortic valve orifice (Fig. 5).

Discussion

Pulsed Doppler echocardiography is of particular benefit in those subjects with mild disease, for whom invasive studies are scarcely justified. Without some objective, independent analyses, clinical diagnoses are in danager of being unchallenged and somewhat arbitrary. Though we,[11 12] and others[13] have validated the results of pulsed Doppler echocardiography by comparison with catheterisation and angiocardiography, a logical case can be made for the superiority of a technique for detecting turbulence, the pulsed Doppler echocardiogram, over these invasive techniques, when the purpose of the study is to evaluate the anatomical origin of a murmur.[14] The pulsed Doppler echocardiogram has the same usefulness—and limitations—as intracardiac phonocardiography, with the major advantage that cardiac catheterisation is not required. Study of the left heart requires arterial cannulation, and the possibility of compromising arterial flow to the leg includes a significant risk of retarded limb growth.[8]

The conventional echocardiogram performed relatively well in confirming the presence of abnormal anatomy of the aortic valve; a positive finding of a dilated aortic root and an eccentric orifice is useful to corroborate the clinical diagnosis of aortic valve disease. However, the absence of these echocardiographic abnormalities does not rule out the aortic valve as the origin of abnormal turbulence, since eight of the 29 patients with aortic turbulence had no echo abnormalities. The possibility exists that these eight patients had no heart disease, and that the murmurs were "innocent". Stein and Sabbah,[15] indeed, assert that most innocent murmurs originate in the aorta, rather than at the pulmonary valve. They used invasive intravascular phonocardiography in 10 adults; only four of their patients had *any* murmur audible, and only two had a grade 2/6 murmur. These two subjects were 50 and 69 years old, which puts them at 37 and 47 per cent risk of having aortic murmurs according to Bruns and Van der Hauwaert.[16] An unrecognised bicuspid aortic valve would have an even higher probability of calcification at that age.[7] In fact, the 69-year-old *did* have mild aortic stenosis, and not a "functional" murmur: the authors' Fig. 3 shows a withdrawal pressure curve with a gradient across the valve of 9 mmHg. Furthermore, none of the 10 patients in their series had an energy level even one-half the 3 ergs/s per cm^2 which they claimed earlier[17] would make the turbulence audible at the chest wall. In short, we do not believe that their data support their contention that the ordinary innocent murmur is aortic in origin.

The pulsed Doppler diagnosis of abnormal turbulence in the eight patients with no M-mode echocardiographic abnormalities we believe reflects mild, obstructive dysfunction of the aortic valve, and not innocent murmurs. In the past two years, with the present personnel and equipment, we have analysed the aortic flow in 1039 children suspected of heart disease because of praecordial mumurs in all. We found 97 records free of any turbulence, 772 with turbulence in various chambers and vessels other than the aorta, and 170 with turbulence in the aorta. Thus, we do not believe that aortic turbulence is normal, or compatible with an innocent murmur. It is also well to remember that only three-quarters of patients with known bicuspid aortic valve have significant asymmetry or eccentricity on echocardiography,[18] and very few, if any, bicuspid aortic valves could be completely unobstructive, because the cusps are tethered, stretching across the valve ring.[19]

Though we assert that pulsed Doppler echocardiographic turbulence is not compatible with the diagnosis of an innocent murmur, the absence of such turbulence leaves unanswered the question of origin of the soft innocent murmur. We believe that an innocent ejection murmur may be produced by right ventricular ejection, but with insufficient disturbance of flow to produce turbulence detectable by the pulsed Doppler echocardiogram, considering the proximity of the outflow tract of the right ventricle to the chest wall, in relation to the usual site of maximal intensity of the murmur. Another possible source of the innocent murmur may be retrograde transmission from a carotid bruit.[20]

Recently, absence of high frequency flutter of the aortic leaflets during systole has been suggested as "distinguishing a functional murmur from one resulting from organic valve stenosis".[9] We retrospectively examined for this phenomenon in a subset of 24 of our patients. This set included six normal subjects and 18 with aortic stenosis determined by pulsed Doppler echocardiography; we could positively identify flutter in five of the six normals, but also in 10 of the 18 patients with aortic stenosis. It is then obvious that the presence of flutter in no way rules out aortic stenosis.

The criteria for diagnosis of aortic stenosis based on auscultation performed well, in terms of specificity, 26 of 30, or 87 per cent. However, these clinical criteria were not as successful for sensitivity, missing three out of the 10. There were two of the criteria that were misleading in a few instances. Transmission of a basal murmur to the carotids was regarded as favouring aortic stenosis, but we found that pulmonary stenosis could transmit to the neck, and several normal children had a combination of an innocent ejection murmur and a coincidental carotid bruit.[20] The second fallible assumption was that a brief diastolic bruit at the left sternal border, in a patient with no pulmonary hypertension, was a result of aortic regurgitation. We have unequivocal documentation of the occurrence of pulmonary regurgitation in children with no other cardiopulmonary disease.

Considering the presence of a bicuspid aortic valve in approximately 1 per cent of the normal population,[21] many of these patients are probably not diagnosed at present, and do not receive appropriate protection against infective endocarditis. Since the complications are severe, though infrequent,[22 23] improved non-invasive means of accurate diagnosis and follow-up are needed.

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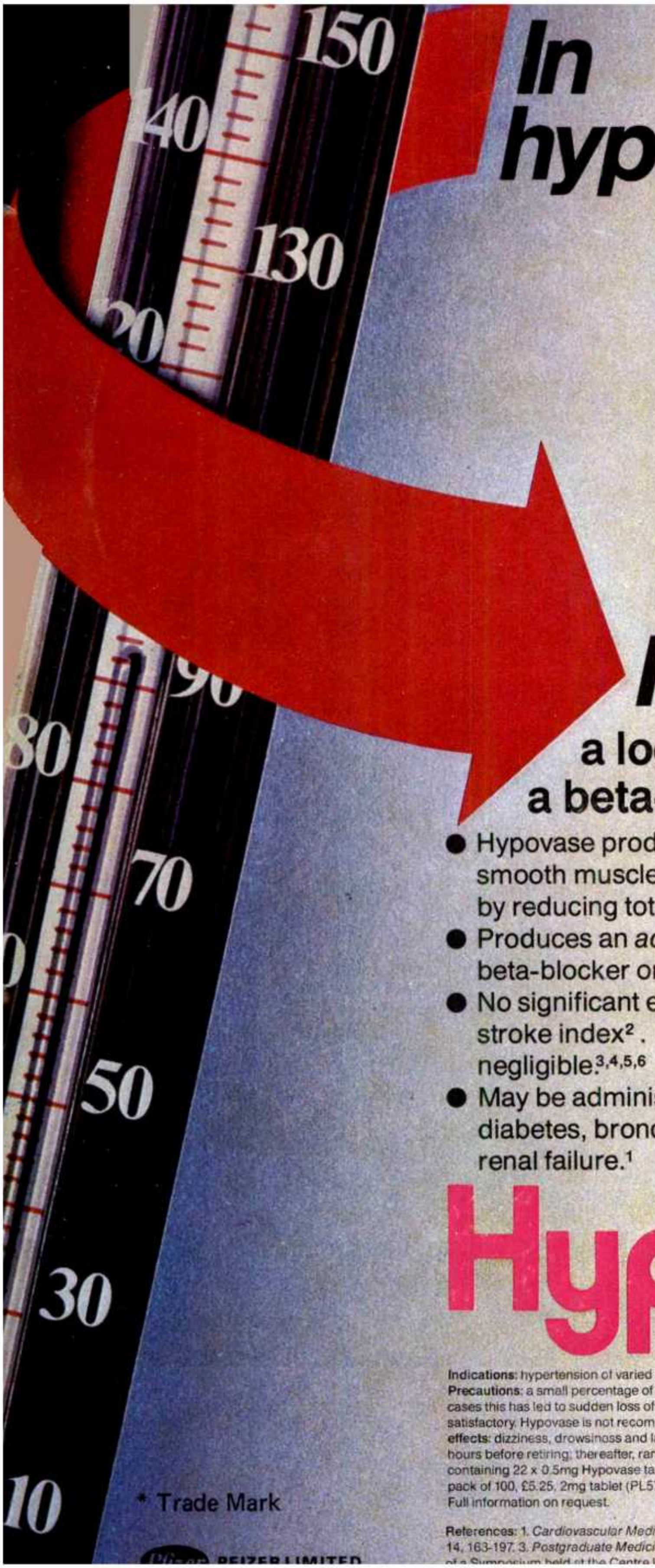

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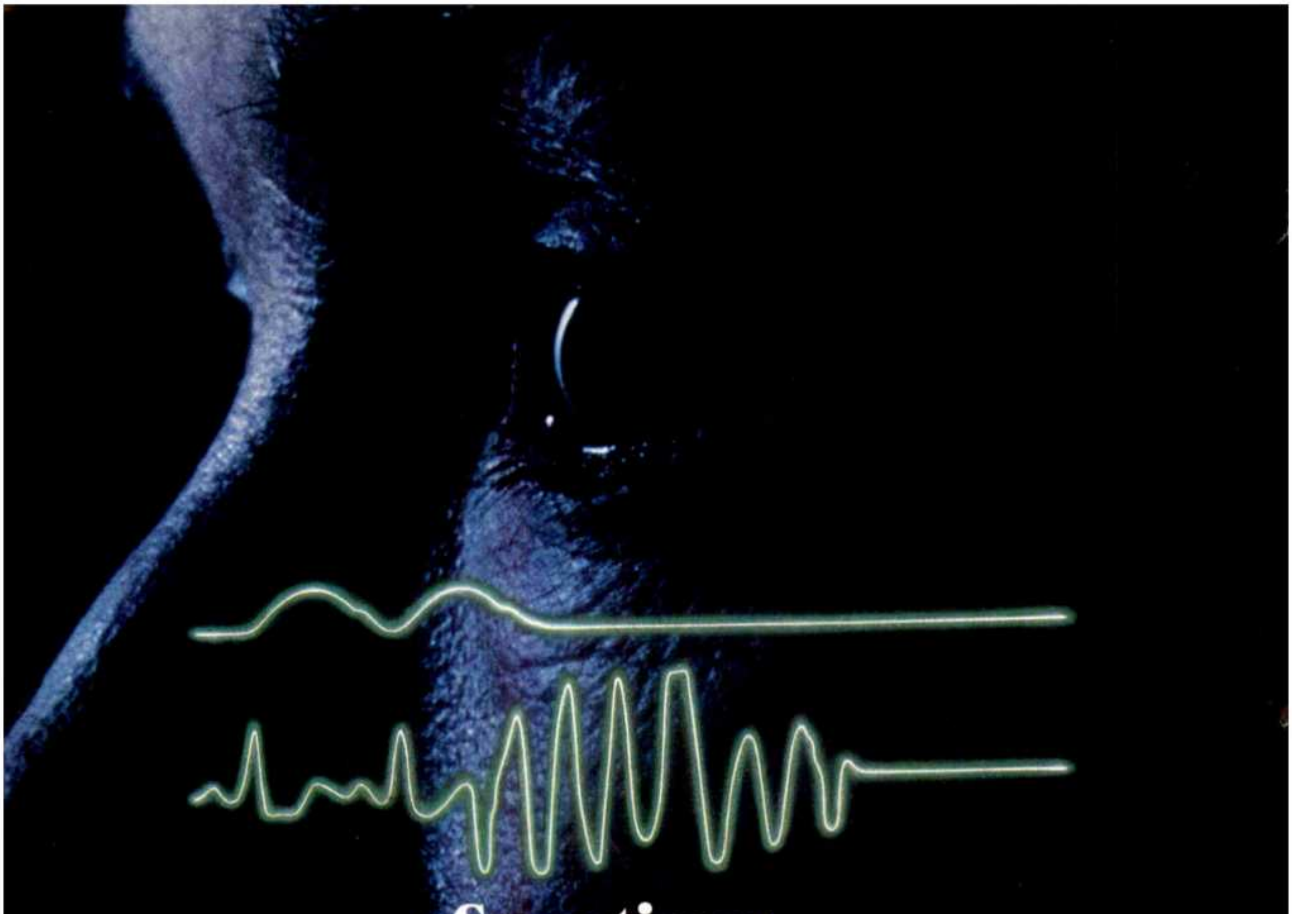

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Br Heart J 1980; **43:** 629–47

Fate of patients with fixed subaortic stenosis after surgical removal

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SUMMARY Thirty-nine consecutive patients, aged 5 to 57 years, were followed for two to 15 years with serial haemodynamic studies after removal of fixed subaortic stenosis, which was never a "membrane". Two late deaths occurred, one sudden and one in congestive failure. Of 37 survivors, 25 were asymptomatic and could be classified as good or excellent if judged by well-being. Seven were symptomatic, two having had reoperation for fixed subaortic stenosis, and four needed long-term pacing.

Evaluation, including the effect of isoprenaline, showed important dynamic obstruction in 17, five of whom redeveloped fixed obstruction. Seven had congestive features without outflow gradients, and 14 had neither congestion nor outflow obstruction. Complete assessment therefore confirmed that only 14 (36%) were haemodynamically satisfactory; two of them had permanent pacing, and four had had aortic valve surgery.

Fixed subaortic stenosis should be removed early, when diagnosed, and completely before secondary myocardial changes occur. Patients however "well" need regular supervision and early haemodynamic assessment. The aortic valve, whether repaired, replaced, or untouched, remains a site for infective endocarditis for life.

The fixed subaortic stenosis removed at operation may not be present in that form at birth, but acquired secondary to other congenital abnormalities which remain in the patient.

Fixed subaortic stenosis, which is usually classified as a congenital lesion, takes the form of a crescentic shelf or complete ring. It is often eccentric, attached to the anterior cusp of the mitral valve and/or the left coronary cusp of the aortic valve, 1 to 2 cm below the aortic valve. Surgical excision is relatively simple and should, theoretically, relieve the haemodynamic problem. However, after surgical treatment was established, it was soon noted that results were unpredictable.[1–4]

It appeared from several different series that despite removal of the fixed part of the obstruction the cardiac muscle could continue to behave physiologically like hypertrophic cardiomyopathy[5–7] and that there might be an overlap between the conditions.

The clinical and haemodynamic state of long-term survivors after resection of fixed subaortic stenosis has now been examined with sequential studies. From these results it may be necessary to change our views on pathogenesis, timing, and technique of surgery.

Subjects

In the National Heart Hospital between 1964 and 1977, 40 patients, aged between 5 and 57 years at the time of operation with cardiopulmonary bypass, had excision of a fixed (discrete) subaortic stenosis.

Normothermic cardiopulmonary bypass through a median sternotomy was used with partial or total coronary perfusion. The ascending aorta was opened through a vertical incision and the aortic valve was inspected and then retracted to expose the subaortic area. Valvotomy (3) or excision (4) before replacement was done when necessary. The ring or shelf was then excised completely, taking care to avoid damaging the anterior cusp of the mitral valve. After restarting coronary perfusion, the subvalvar muscle of the ventricular septum covered with thickened cream-coloured endocardium was inspected and usually seen to be bulging abnormally into the left ventricular outflow tract. In 34, a deep incision was made into the apex of

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* Research Secretary supported initially by a one-year grant from the British Heart Foundation and subsequently by an anonymous donor.

Received for publication 14 November 1979

the bulging septum, and in 25, a wedge of muscle was removed. In the past two years the technique has been changed in view of the late results. Now, all thickened endocardium is stripped off by blunt dissection from the bulging ventricular septum. This peels off like a skin to which the fixed obstructing subaortic shelf or ring is attached and ensures removal of all visible fibro-collagenous material. After the aortotomy had been sutured all the patients came off bypass easily except the one who died. Simultaneous needle pressures from the ascending aorta and left ventricular body were measured when the circulation was stable. The present policy is to return to bypass if the gradient exceeds 40 mmHg and resect more muscle or excise the whole root, depending on the pathological anatomy.

After operation, patients were examined at six monthly or annual intervals with repeated electrocardiograms, phonocardiograms, and chest radiographs. Most patients in the last three years had M-mode echocardiograms which will be discussed in another report.

Recatheterisation was performed one to 12 years after operation when agreed to by patient and referring physician; 11 patients had two postoperative studies and one had three. After reoperation further postoperative catheterisation was done under the same conditions. Gradients between the aorta and left ventricular body were measured at rest, on withdrawal of the catheter across the outflow tract, and after isoprenaline infusion sufficient to raise the heart rate to 130 to 160 per minute. Left ventricular angiograms with 0·5 to 1 ml/kg Conray 420 injected slowly were recorded on biplane Elema still films or cine angiograms in the left anterior oblique or lateral and anteroposterior views. Routine aortograms were also performed to assess aortic regurgitation.

Ten patients were not reinvestigated, either because the referring physician refused (six), death (one), or the patient refused (three). The present clinical state is known in all patients.

For simplicity, the electrocardiographic changes of left ventricular hypertrophy from the resting record immediately before operation were graded 1 to 4:

Grade 1: Increased voltage of R in V6, above 30 mm, with normal ST segments and upright T waves.

Grade 2: Increased voltage and flattening of T waves/or ST depression in the left ventricular and/or anterior chest leads.

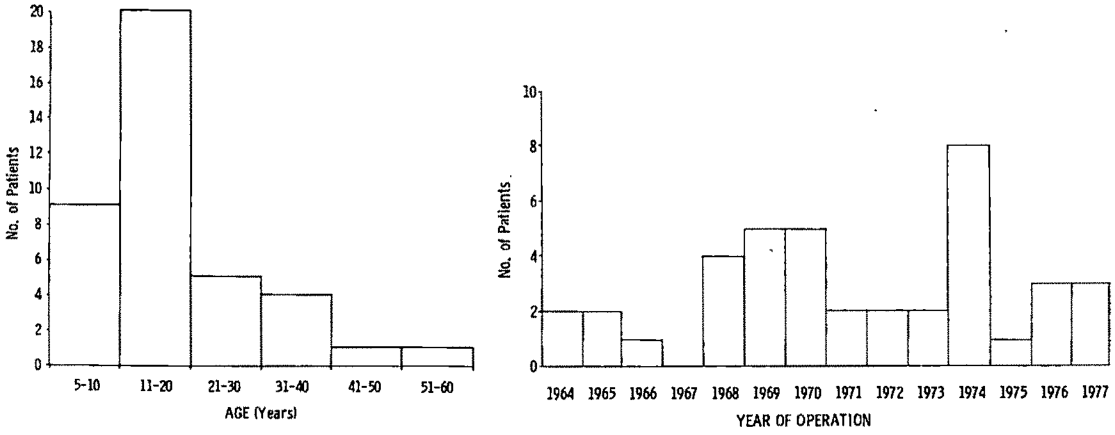
Grade 3: T inversion in the left chest leads.

Grade 4: Deep T inversion with ST depression of 3 to 8 mm in left ventricular leads.

Preoperative state of patients

CLINICAL

The age distribution of the patients at the time of operation and the year of operation are shown (Fig. 1a and 1b). The youngest was 5 years and the eldest was 57 years; 20 were in the second decade (23 male and 17 female). Twenty-seven had symptoms and 13 were symptom free. Left ventricular



(a) (b)

Fig. 1 (a) *Age when fixed subaortic stenosis removed in 40 patients.* (b) *Calendar year when fixed subaortic stenosis removed in 40 patients.*

hypertrophy on the electrocardiogram was present in 38, and two, aged 49 and 57 years, had left bundle-branch block. All were in sinus rhythm. There was no correlation between presence or absence of symptoms and the height of the peak systolic gradient or degree of left ventricular hypertrophy (Fig. 2). Usually patients with grade 4 changes had symptoms and resting gradients above 75 mmHg; an exception was one 9-year-old boy who appeared in left ventricular failure with a large infected duct and a gradient of only 35 mmHg.

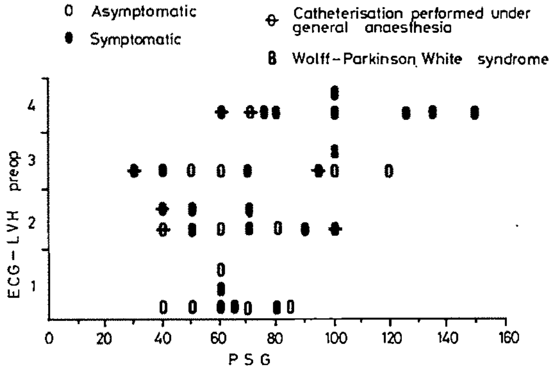


Fig. 2 *Electrocardiographic grade of left ventricular hypertrophy (1–4) (LVH) related to preoperative peak systolic gradient (PSG) across the left ventricular outflow tract in symptomatic and asymptomatic patients with fixed subaortic stenosis.*

Murmurs of aortic regurgitation were audible in 36 patients and trivial aortic regurgitation was noted on aortography in a further two. Angiography confirmed trivial regurgitation in the majority, but clinical assessment of the severity of aortic regurgitation was difficult because of the frequently found jerky pulse and rise in the systolic pressure. Two patients with previous bacterial endocarditis had severe aortic regurgitation. One of the two patients without an immediate diastolic murmur was found to have a completely normal aortic valve and the other had a bicuspid aortic valve.

Important cardiac enlargement on the chest radiograph (CTR > 55%) was seen in five patients: the only two patients with a left-to-right shunt from a duct and failure, two patients over the age of 40 years, and the 29-year-old with a haemolysing Starr valve. A pronounced left ventricular contour at the apex was obvious in most, but low (caudal) post-stenotic dilatation of the ascending aorta was only seen in seven patients. The chest radiograph was not helpful in differentiating subaortic stenosis from other forms of congenital aortic stenosis.

The initial indications for removal of the subaortic stenosis were electrocardiographic changes of left ventricular hypertrophy (grade 1 to 4) and/or the demonstration of a peak systolic gradient at rest above 50 mmHg, symptoms in association with either of the previous criteria, or failure from associated aortic regurgitation or large duct. In the past three years, fixed subaortic stenosis was removed when diagnosed and confirmed by angiography and gradient measurement, irrespective of severity or whether or not there were associated electrocardiographic changes.

INVESTIGATION

At preoperative catheterisation resting gradients were measured in 34 patients. The gradients were found to be labile, being lower with general anaesthesia (six), higher with agitation, and increasing conspicuously with isoprenaline in three with gradients below 60 mmHg. Isoprenaline was not given to others before operation. The gradient increased after a single ectopic beat with an increase in both aortic and left ventricular systolic pressures as in fixed obstruction. The end-diastolic pressure in the left ventricle was raised (15 to 20 mmHg) in four patients, two with signs of heart failure and the other two with breathlessness. Unfortunately, no haemodynamic studies were done in the two older patients with established left bundle-branch block; each had been referred for aortic valve replacement despite the absence of radiological calcification.

In 19, the subaortic obstruction was difficult to see, and in 10 a "membrane" was seen on *x*-ray films. Left ventricular septal muscle and free wall muscle was grossly and irregularly thickened in 16 patients (Fig. 3a and b). Regular concentric hypertrophy with septal hypertrophy was obvious in 28 (Fig. 4A and B). The aortogram showed characteristic slow opening of the aortic valve cusps which were visible, in the absence of congenital fusion, in mid-to late systole, with uneven concavity towards the lateral. Clinically unsuspected fixed subaortic stenosis was diagnosed correctly from the aortogram in three patients from the characteristic appearances of the aortic valve movement (Fig. 5a). Doming of a mildly stenosed aortic valve above a subvalvar obstruction was recognised in seven; thickening of the valve was frequently noted. Aortic regurgitation was confirmed in 38 patients and frequently outlined the fixed subaortic obstruction (Fig. 5b) better than left ventricular angiography. The ascending aorta was dilated in 15, small in 23, and associated with slight supravalvar waisting in 12.

PREGNANCY AND FAMILY HISTORY

Three patients who also had a duct were products of pregnancies complicated by rubella. One other patient's mother was diabetic. There was a family history of congenital heart disease in first degree relatives in two; in one a brother died suddenly with hypertrophic cardiomyopathy and another has a daughter with a long aortic ejection systolic murmur. A specific family study was not made.

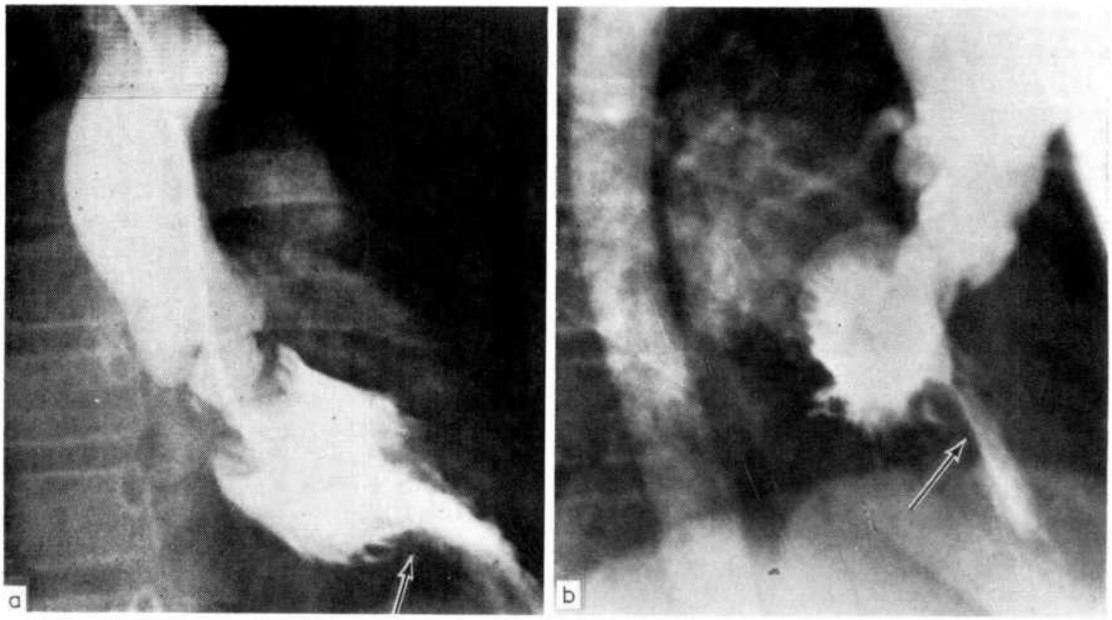


Fig. 3 *Preoperative left ventriclar angiograms from boy, operated on in 1974 aged 11 years, with fixed subaortic obstruction caused by crescent of tissue and thickened endocardium over severely bulging ventricular septum. Large lumps of eccentrically hypertrophied muscle are present* (arrows). *This patient maintained clinical and haemodynamic obstruction for five years.* (a) *Anteroposterior view.* (b) *Lateral view.*

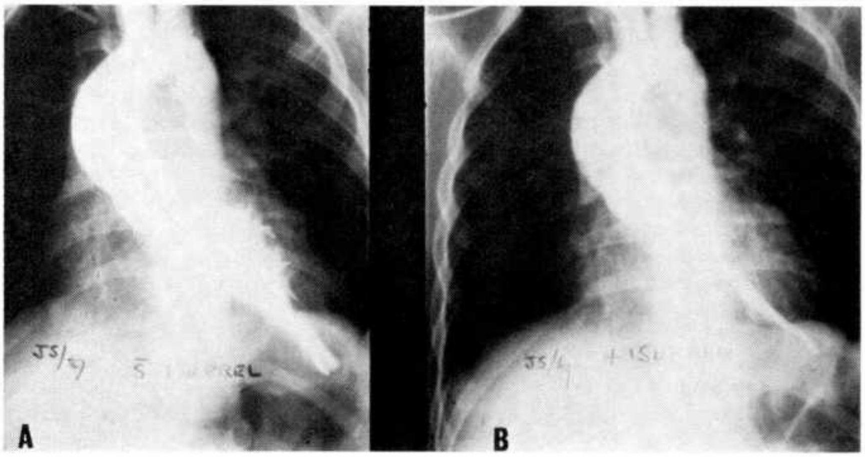
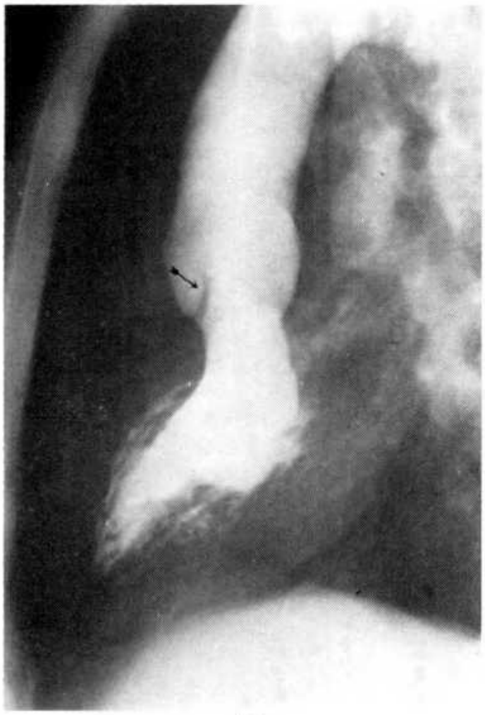


Fig. 4 *Diffuse concentric hypertrophy shown on anteroposterior view of left ventricular angiogram from 6-year-old boy with fixed subaortic stenosis, grade 4 LVH and peak systolic gradient 70 mmHg.* (A) *Before isoprenaline.* (B) *After isoprenaline infusion. He maintained a good haemodynamic result seven years later with regression of LVH and resting gradient 0 mmHg rising to 20 mmHg with isoprenaline.*


(a)

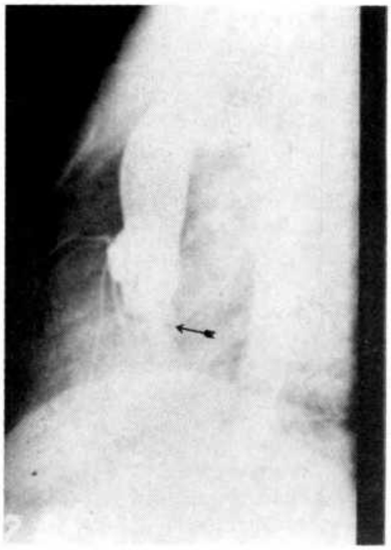

(b)

Fig. 5 (a) *Systolic frame from lateral view of left ventricular angiogram showing characteristic movement and visibility of "normal" aortic valve with fixed subaortic stenosis beneath* (not obvious). (b) *Aortogram* (lateral) *from 12-year-old boy with fixed ring obstruction outlined* (arrow) *beneath regurgitant aortic valve.*

CONGENITAL CARDIOVASCULAR LESIONS

Twenty-four patients (60%) had other congenital abnormalities in the cardiovascular system (Fig. 6). Ventricular septal defects were documented by angiography in seven patients; three closed spontaneously before the operation for the subaortic stenosis. The fibrous tissue closing the defect was attached to the subaortic stenosis which was proximal or contiguous with the ventricular septal defect, and there is evidence to suggest that the subaortic obstruction formed or progressed in the period when the ventricular septal defect was closing. In one child the ventricular septal defect had been closed surgically six years earlier leaving the undiagnosed fixed subaortic obstruction—the child nearly died in the postoperative period and suffered myocardial damage which was probably contributory to his sudden death a year after resecsection of the subaortic stenosis.

Coarctation at the classic site was resected in four patients, one aged 5 months, one aged 8 months, and two at 4 years; a further two had a mild untreated coarctation. Ten patients had a documented persistent duct, ligated earlier in nine and closing spontaneously in the first decade in one.

The aortic valve was congenitally abnormal in nine: four had a true bicuspid aortic valve, four a "tricuspid" valve with a rudimentary fused anterior commissure, and one had a small valve in which two cusps were attached higher than usual.

In only 16 patients (40%) was there no other congenital abnormality discovered in the heart or great arteries. The subaortic stenosis had the same morphology in those with and those without congenital abnormalities.

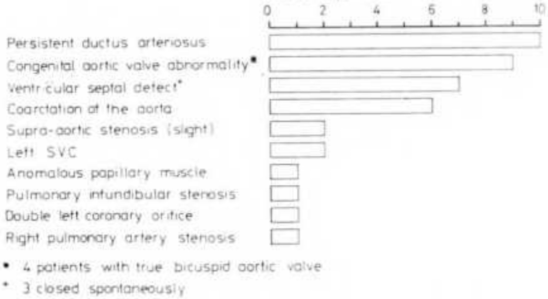


Fig. 6 *Associated congenital abnormalities in the cardiovascular system in 40 patients with fixed subaortic stenosis.*

ACQUIRED PATHOLOGY IN AORTIC VALVE

The aortic valve showed acquired pathological changes in a further 20 (50%); thickening of cusp edges or one cusp (19), perforated cusps (3), and in one patient, aged 57 years, the valve was seen to be thin and floppy. In one patient aged 29 years a destroyed valve from bacterial endocarditis was replaced with a Starr valve—it is not known if there was a basic congenital abnormality in this patient.

The aortic valve was said to look "probably normal" in 11 patients (27·5%), aged 5 to 32 years, despite an aortic diastolic murmur in nine. Most of these had slight thickening in the centre of one cusp which remained pliable.

OTHER OPERATIONS AT TIME OF RESECTION OF SUBAORTIC STENOSIS

Four patients had aortic valve replacement: a pulmonary autograft in one, a Starr valve in one, and a "fresh" aortic homograft in two. Other operations included closure of ventricular septal defect in three, open aortic valvotomy in three, resection of right-sided fixed ring infundibular stenosis in one, ligation of persistent ductus arteriosus in one, and relief of supra-aortic stenosis in one. The 12-year-old girl in failure with a duct and slight coarctation and a tight fixed subaortic obstruction developed ventricular fibrillation during the thoracotomy for the duct and so the incision was extended and bypass instituted to resect the subaortic obstruction after duct closure.

ANATOMY OF SUBAORTIC STENOSIS

Conventional classifications used by others[3 4] have not been used here as we believe them to be a source of confusion and misinterpretation. Firstly, because there is little evidence that the lesion is "discrete" except in the minds of radiologists and the surgeon who resects it, and a membrane by definition "a thin pliable sheet-like tissue"* was never encountered. A simple description of what was found has been used. Whether it was near or separated from the aortic valve depended in part on its completeness, its obliquity, and the distribution and hypertrophy of muscle bordering the outflow tract. Since only one died, there was no opportunity to measure and quantify this aspect which has recently received attention,[8] and is likely to be relevant to pathogenesis and postoperative evolution of the lesion.

Eighteen had a complete ring, which could be described as a collar. This was excised *in toto* in seven (Fig. 7a). In three, the whole ring was close to the aortic valve but in the rest it had the same morphology but lay obliquely and not parallel to the valve, appearing to be 0·5 to 1·5 cm beneath the valve, depending upon which part of the aortic valve ring the measurements were made from or assessed. In most of these oblique rings only part was close to the aortic valve lying in the "space" between the aortic and contiguous anterior mitral cusp. In others and in some with crescents, there appeared a wider area than usual between the aortic and mitral cusps which may have accounted for the apparent lowness of the obstruction. Excessive bulging of the ventricular septum, frequently covered with thickened "wash leather" endocardium, to which the obstruction was attached, occurred in 15, and was unrelated to proximity of the ring to the aortic valve.

In the other 22 patients there was a crescentic shelf projecting into the outflow (Fig. 7b); 19 had severe septal bulging. There was calcium in the crescentic web in one girl aged 14 years and in only three was the crescent close to the aortic valve. In the rest it was oblique and separated from the valve ring by about 0·5 to 1·5 cm, as were the rings described above. One shelf appeared to be vascular and inflamed without clinical signs of active endocarditis. The subaortic obstruction was often rolled and uneven with areas of increased denseness in both the crescents and rings.

HISTOLOGY

The obstructing ring or shelf was usually referred to as "fibrous". It was, in fact, a composite of different tissue cells varying from patient to patient. Often there was a large percentage of irregularly orientated acellular dense collagen fibres. Elastic fibres, thin, short, and irregularly arranged, were

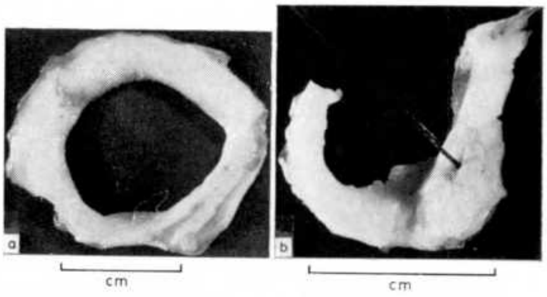


Fig. 7 (a) *Complete ring removed from beneath the aortic valve from a 21-year-old man. The angiogram was reported to show a "typical membrane".*
(b) *Crescentic shelf forming subaortic obstruction, attached to thickened endocardium stripped off the bulging ventricular septum, from a 13-year-old girl.*

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* Shorter Oxford English dictionary, 3rd edition.

seen and these varied in density and distribution in different blocks from the same patient. Three patients had a large amount of elastic tissue.

In the majority of sections, elongated nuclei resembling fibroblasts were scattered sparsely, and in some sections they merged into large acellular areas and the nuclei became shorter and plump within cytoplasm which, with trichrome stains, had the staining characteristics of smooth muscle. Whether there was a ring or crescent, the histology was the same.

Vascularity was usually absent but occasional sections showed a rich network of capillaries with some arterioles containing an elastic network.

Biopsies of septal muscle were small and showed mild to moderate interfascicular fibrosis with simple hypertrophy. Classic dysplasia of the myocardium in wide areas was not seen.

Results

DEATHS

One operative death occurred in a 29-year-old man with a previous Starr valve replacement for an infected aortic valve elsewhere. At emergency reoperation a tight fixed subaortic fibromuscular stenosis was removed from beneath the Starr valve but the heart failed to come off bypass.

Two late deaths occurred in the 39 survivors; one man died aged 49 years when a ring subaortic stenosis was removed, though he had left hospital symptomatically improved but with persistent left bundle-branch block and cardiomegaly; he died five years later in congestive heart failure after the onset of atrial fibrillation. Neither a necropsy nor postoperative haemodynamic studies were done. The other death was in an asymptomatic boy aged 14 years, one year after operation, during a game of football which he had been advised not to play.. Postoperative studies one year after operation showed that the left ventricular end-diastolic pressure was 19 mmHg, with neither outflow gradient nor aortic regurgitation. Unfortunately, the coroner did not consider there was need for necropsy.

SURVIVORS

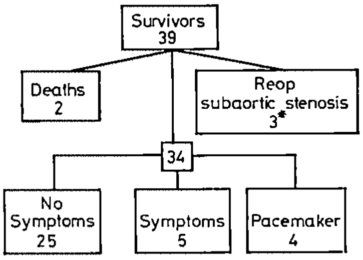
The state of 37 survivors two to 15 years after operation has been summarised (Fig. 8). Twenty-five had no symptoms, considered themselves well, and were undertaking full normal activities. Five had symptoms, either a return or persistence of angina or dyspnoea, and two had paroxysmal tachycardia. Four had permanent pacemakers which required the usual supervision and changes.

Three types of physiological behaviour were found in each group of patients and designated as dynamic obstruction, "congestive", or normal. Patients were considered to have dynamic obstruction when isoprenaline caused a gradient across the left outflow tract greater than 60 mmHg, together with characteristic features suggestive of obstruction such as long ejection systolic murmur, jerky pulse, and clear aortic second sound. Since no patient had significant aortic valve or supravalve stenosis, the dynamic obstruction was assumed or shown to be at subvalvar level, usually over a diffuse area. Fixed obstruction was accepted when resting gradients were above 50 mmHg, always associated with a high isoprenaline response, physical signs of subaortic stenosis, and a visible obstruction on angiography (Fig. 9a and b).

Patients were classified as having a "congestive" myopathic left ventricle when the end-diastolic pressure in the left ventricle exceeded 10 mmHg (pre A) with low ejection fractions below 55 and/or radiological, and/or symptomatic features of congestion. Patients evaluated as truly good ("normal") (14) had none of the above haemodynamic findings; there was maintained improvement of the electrocardiogram, absence of symptoms, and no severe aortic regurgitation.

Fixed obstruction—reformed and reoperated

Fixed obstruction appeared two to nine years after the first operation in four patients and is probably present in a fifth. The four were operated on by the same surgeon who found again thickened endo-

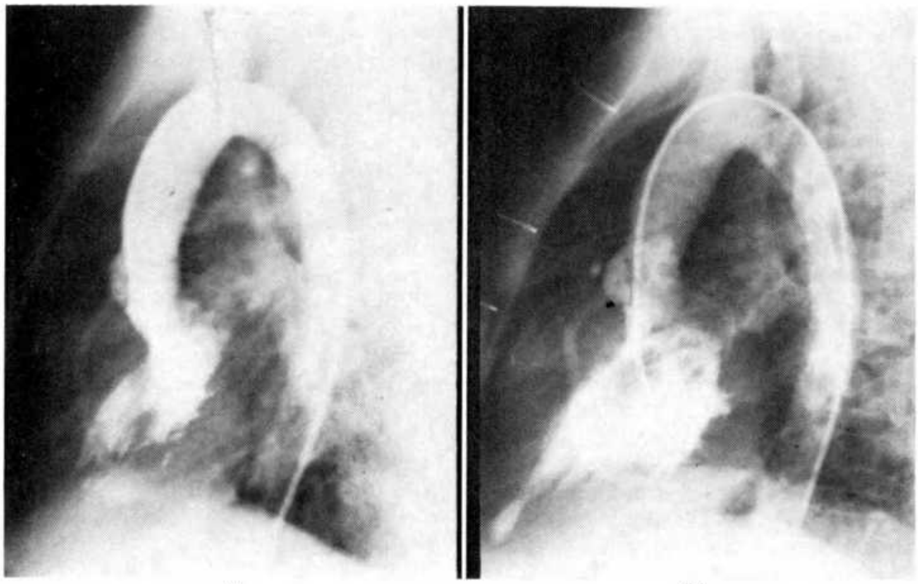


	No Symptoms	Symptoms	Pacemaker
Dynamic obstruction	9	3	1
Fixed obstruction	1*	1	–
↑ LVEDP	2	1	1
Important aortic regurgitation	1	-	-
Good	12	–	2

Fig. 8 *Summary of state of 39 survivors two to 15 years after resection of fixed subaortic stenosis. Correlation with haemodynamic state. LVEDP, left ventricular end-diastolic pressure; *, patient operated on after paper accepted for publication*

cardium attached to a protruding shelf which had previously been excised. The dynamics of these five patients have been summarised (Table 1). The electrocardiogram worsened after initial improvement. Three were symptomatic.

At the first cardiac catheterisation after operation all had an intense response to isoprenaline. In case 1 the obstruction probably had not been adequately relieved, as a long muscular tunnel persisted allowing a resting gradient of 83 mmHg one year later. The patient had been in failure at the time of the first operation because of an associated large duct.



(a) (b)

Fig. 9 *Lateral views of left ventricular angiograms before a fixed subaortic ring was resected* (a), *and five years later when a tunnel obstruction had developed* (b). *After the first operation the resting gradient across the outflow was 20 mmHg, the aortic valve was normal, and the electrocardiogram improved. Four years later syncope and angina returned with worsening of the electrocardiogram. At reoperation the fixed shelf had reaccumulated over a long fixed fibromuscular obstruction.*

Table 1 *Peak systolic gradients across the left ventricular outflow tract before and after operation in five patients who redeveloped fixed subaortic stenosis*

Case no.	*Age at opn.*	*Other lesion*	*Peak systolic gradient (mmHg)*					*Age at reop.*	*Peak systolic gradient after second operation*			*Comment*
			Preop. rest	*Immediately postop.*	*Year*	*Rest*	*Isoprenaline*		*Year*	*Rest*	*Isoprenaline*	
1	12	Aortic stenosis, duct, mild coarctation	80	—	1½	83	—	15	1	20	80	Re-resection of subaortic stenosis LVEDP ↑
									3	8	8	
					1	25	140					
2	11	—	120	30				20	6/12	5	50	Aortic root replaced
					9	55	125					
					2	18	56					
3	10	—	60	10				15	—	—	—	Aortic root replaced
					4	50	100					
					1	85	185					
4	15	—	90	50				—	—	—	—	Aortic root replaced
					10	60	150					
					1	40*	80*					
5?	11	—	80	5				—	—	—	—	
					9	50	90					

* Catheterisation performed under general anaesthetic. LVEDP, left ventricular end-diastolic pressure.

It is possible that the potential for persistent outflow obstruction had been underestimated at the hurried operation when the left ventricle was dilated after failure and ventricular fibrillation. As the heart, relieved of the volume overload, recovered tonicity the outflow became more obstructed and the fixed shelf part redeveloped quickly as the result of continued persistent turbulence. One other (case 4) had an 85 mmHg resting gradient at the first study, having had a crescent initially removed. At reoperation there was slight fusion of aortic valve cusps and intense subvalvar endocardial thickening and protrusion of a shelf into the outflow. Aortic root replacement with reimplantation of the coronary arteries was done.

The other two patients did not have high resting gradients at the first postoperative catheterisation and so it is difficult to claim that important fixed obstruction had been left behind. Certainly abnormal muscle remained in all and the ascending aorta was not dilated and had a slight supra-aortic narrowing of no haemodynamic significance in three of the five.

In three patients further resection of the subvalvar muscle and redeveloped shelf did not relieve the obstruction and high gradients between the left ventricle and ascending aorta persisted. The whole aortic root was then excised and replaced with a homograft aortic root and valve, with reimplantation of the coronary arteries.[9] This appeared to relieve the obstruction successfully, since postoperative studies six to 12 months later confirmed resting gradients 5 to 20 mmHg, rising to 50 to 80 mmHg with isoprenaline stimulation. Case 1 with a stimulated gradient of 80 mmHg did not have a root replacement.

The fifth patient (case 5) probably has a redeveloped fixed obstruction but it is not visible on the recent angiogram despite the high pressures. He has been treated with propranolol and no longer has new symptoms.

Dynamic obstruction

Seventeen patients (including those who developed fixed obstruction) had haemodynamic evidence of dynamic obstruction and/or physical signs suggesting its presence. Intravenous propranolol in seven altered the signs, making the jerky pulse become normal and diminishing the length of the ejection systolic murmur.

The relation to the age when operated on, the severity of the preoperative electrocardiographic hypertrophy, the postoperative peak systolic gradient measured at operation after resection and at the first postoperative study, and whether or not they had dynamic obstruction are shown (Fig. 10a and b).

The dynamic obstruction appeared to persist more often in those patients who had grade 4 left ventricular hypertrophy before operation. The measurement of the gradient immediately after resection, on the table, did not reflect the subsequent course though those left with gradients over 25 mmHg were more likely to have dynamic obstruction.

Four patients developed angina, syncope, or

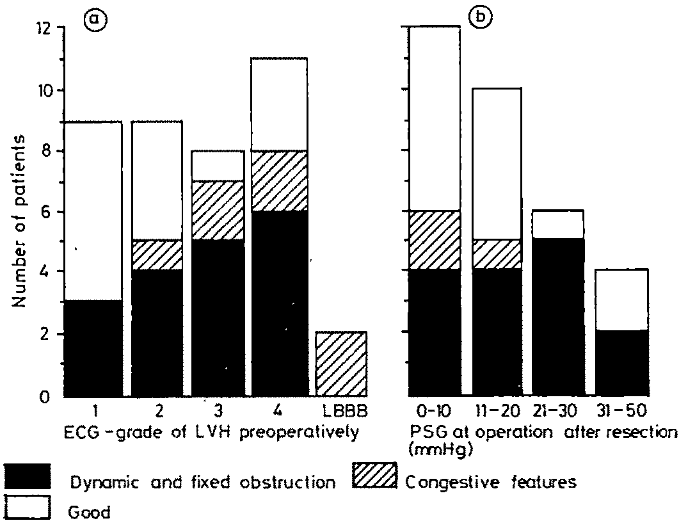


Fig. 10 *Correlation between grade of left ventricular hypertrophy present before operation* (a) *and peak systolic gradient measured immediately after resection of subaortic stenosis on the table* (b) *and the subsequent findings of dynamic obstruction, congestive myopathic ventricle, or normal dynamics.*

dyspnoea which reappeared after a period without symptoms. One who required permanent pacing and studies before implantation of the pacemaker showed how isoprenaline produced a high gradient (Fig. 11a), but when the heart rate was increased by pacing it lowered the gradient (Fig. 11b). Thirteen patients with dynamic obstruction were symptom free and considered themselves well, but in four the electrocardiograms were deteriorating after five years.

Repeated haemodynamic studies showed that in seven of eight patients with high gradients after isoprenaline, the response persisted two to 10 years later (Fig. 12). In one, the resting gradient and response to isoprenaline had diminished eight years later. Three patients with minimal response to isoprenaline remained the same six to 12 years later.

Redevelopment of a fixed obstruction occurred as frequently in those where a ring had been excised as in those with a crescent. Important septal thickening and dynamic bulging was seen in 32 and postoperative dynamic obstruction occurred in 15 of these. However, in seven where the septum was not considered to be unusually bulging and thick, two developed severe late dynamic obstruction with symptoms.

Now, patients with dynamic obstruction and appropriate clinical signs are treated with maintenance propranolol 20 to 40 mg bd. It is too soon to assess the long-term results of this.

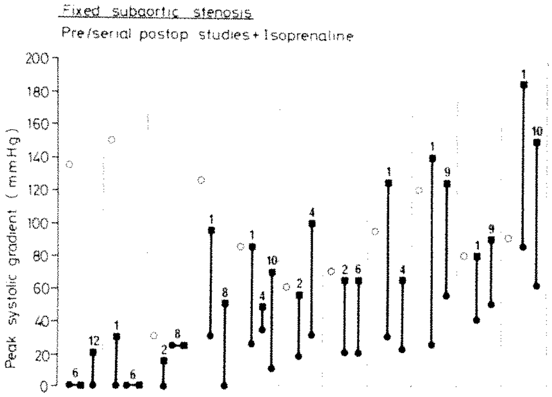


Fig. 12 *Peak systolic gradients across the left ventricular outflow tract at rest before operation* ○, *at the first cardiac catheter at rest* ●, *and after isoprenaline* ■, *and at subsequent studies in 11 patients who had repeated catheterisation after resection of fixed subaortic stenosis. The number above each vertical line is the postoperative year at the time of study.*

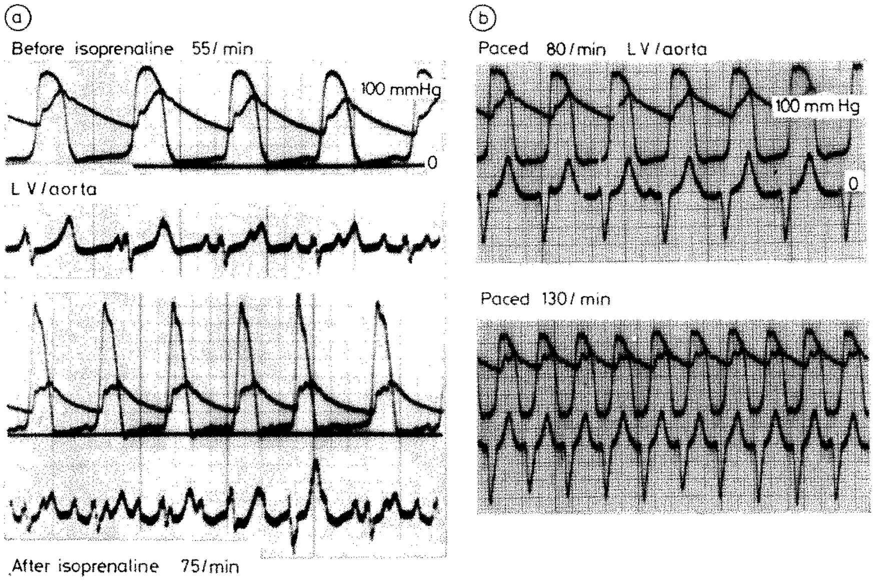


Fig. 11 *Left ventricular outflow gradients measured four months after resection of fixed subaortic stenosis and closure of ventricular septal defect in patient who developed complete heart block at operation.*
(a) Rest. *In block (rate 55/min), gradient 50 mmHg.* Below. *After isoprenaline (rate 75/min), gradient 110 mmHg.*
(b) *Paced 80/min, gradient 25 mmHg. Paced 130/min, gradient 20 mmHg.*

Congestive group

Seven patients had "congestive" features. Two died and one developed heart block and failure six years later and still has cardiomegaly and mild congestive failure. One, a woman aged 38 years, has dyspnoea which is improved by diuretics. One boy aged 11 years at operation was in severe left ventricular failure from an added duct. Ten years later his heart remained large (ejection fraction 55 per cent), with moderate aortic regurgitation but he was improved and symptom free. Two other patients aged 15 and 21 years appeared two to 12 years later with progressive mitral regurgitation and mild congestive features confirmed by investigation. One was a child from a pregnancy complicated by rubella.

This group of seven included three patients over 35 years with larger hearts than those with dynamic obstruction and the two with complete left bundle-branch block before surgery. None had important residual outflow gradients.

Symptomatic

Seven patients developed symptoms and they had either dynamic obstruction (six) with redevelopment of fixed obstruction in three or congestive features in one. Two were reoperated on for fixed obstruction and became symptom free.

Good results—physiological and without symptoms

Of the 14 patients who maintained good physiological dynamics and whose electrocardiograms improved, two had permanent pacing systems and four had had aortic valvotomy or replacement. Thus, only eight patients had not required expert help over a two- to 15-year period. After reoperation a further two can now be added to this group.

Aortic regurgitation

Ten patients had no audible aortic regurgitation after operation; one had had open aortic valvotomy and one had an aortic valve replacement with a homograft—it had been present in nine of these before surgery. Nineteen had grade 1 murmurs and seven had mild regurgitation. Three, already mentioned, had moderate aortic regurgitation, one with a pulmonary autograft, another with a dilated root having had a large duct, and another after open aortic valvotomy. No patient with significant regurgitation had either dynamic or redeveloped fixed subaortic stenosis.

Mitral regurgitation

After operation four patients developed mitral regurgitation which was mild in two and moderate in two. One had trivial regurgitation before operation which increased after; she retained a high gradient on isoprenaline two years after the removal of the fixed obstruction and had been noted to have an anomalously placed papillary muscle at operation. Mitral regurgitation was new in three, appearing one to 10 years later; none had outflow gradients with isoprenaline stimulation, and the left ventricular end-diastolic pressures were raised in all. There was no evidence of congenital lesions of the mitral valve, and it is presumed that the mitral regurgitation was secondary to left ventricular dysfunction.

Electrocardiogram

The changes in the electrocardiograms have been summarised (Fig. 13). Left ventricular voltage reduced usually by the end of the first postoperative year.

In four, the electrocardiogram improved initially and then deteriorated four to eight years later and all these had dynamic or reacquired fixed obstruction.

In the first few months the T waves became sharply inverted over the left ventricular leads

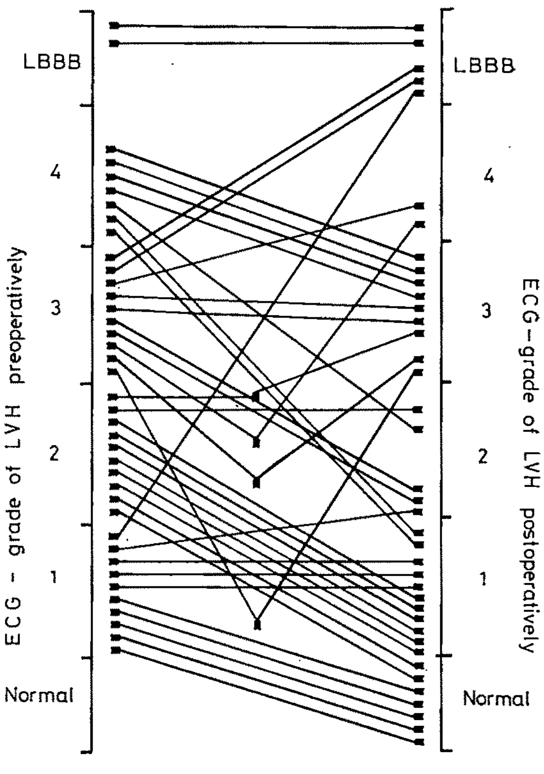


Fig. 13 *Grade of left ventricular hypertrophy before and after, as assessed at most recent attendance (maximum time from surgery).*

presumably in relation to myopericarditis. This usually changed after six months and so assessment of the electrocardiogram was only made after this period.

Left anterior hemiblock developed after operation in five. It was unchanged in two.

Right bundle-branch block appeared after operation in four, three of whom had the right ventricle opened.

New left bundle-branch block was caused by operation in three, aged 12 to 35 years. These all had muscle resection and had no gradients across the outflow at rest or after isoprenaline stimulation. Transient left bundle-branch block appeared for one to four weeks after operation in five.

Complete heart block

Three of 39 patients, aged 8, 16, and 31 years, acquired complete heart block at operation with heart rates of 40 to 50 per minute which were associated with cardiac failure in two.

Two of the three patients had a small ventricular septal defect closed from the right ventricle at the same time as the subaortic stenosis was removed from the outflow. One also had resection of a fixed subpulmonary stenosis.

The third patient, in whom a previously documented ventricular septal defect had closed spontaneously, developed bacterial endocarditis at the age of 31 years resulting in a destroyed aortic valve. At operation four months later a fixed subaortic stenosis was removed and the aortic valve was replaced with a homograft. The residual gradient after operation on the table was not measured; 2:1 heart block returning to sinus rhythm occurred, but three weeks after operation a lithium iodide demand pacemaker was inserted because of Adams-Stokes attacks. He returned to sinus rhythm three years later and his pacemaker is not functioning. He has no evidence of residual fixed or labile obstruction. The heart size is normal and there is trivial aortic regurgitation.

Four years after resection, complete heart block developed in a patient aged 57 years at operation. He had left anterior hemiblock with left bundle-branch block before operation which was unchanged with prolonged PR interval after operation. He has a permanent pacemaker and is in controlled failure 15 years after operation. The state of his coronary arteries is not known.

Other rhythm disorders

Six patients had recurrent ventricular ectopics at rest, found on the routine electrocardiogram. Three of the patients had dilatation of the left ventricle with a raised end-diastolic pressure and one of these died suddenly. The other, a girl, had moderate subaortic obstruction with a gradient of 50 mmHg after isoprenaline eight years later but is otherwise well.

Supraventricular tachycardia recurred in a girl who required reoperation for fixed subaortic stenosis (case 1). She still has the attacks which are now less troublesome than previously. Another girl with Wolff-Parkinson-White syndrome continues to have short attacks controlled by propranolol 120 mg/day.

One other boy had nodal escape beats. Atrial fibrillation causing failure and death occurred in one man aged 49 years.

Pregnancies

Four patients had five successful pregnancies after operation. One had a spontaneous abortion at 10 weeks and another had a termination. None had cardiac problems during the pregnancies and all the children are normal. The postoperative haemodynamics and electrocardiographic state are shown in Table 2. The presence of labile obstruction

Table 2 *Summary of postoperative left ventricular/aortic peak systolic gradients in four patients who completed five pregnancies successfully*

Age at opn. (y)	*Postop year pregnancy*	*Postoperative haemodynamics*				*Duration of follow-up (y)*
		Year	*Peak systolic gradient*		*Grade of LVH on ECG*	
			Rest	*Isoprenaline*		
11	8	2	20	65	2	11
		6	20	65	3	
15	5, 7	1	85	185	1	11
		10	60	150		
24	2	Signs of obst + aortic regurgitation				4
12	9	1	55	140	1	9

LVH left ventricular hypertrophy; Obst, obstruction.

is not a deterrent to successful pregnancy. Propranolol was not given to any during the pregnancy.

Infective endocarditis

No patient had infective endocarditis in the postoperative period. All had careful protection for dental manipulations and extractions.

POSTOPERATIVE INVESTIGATION: SUMMARY OF FINDINGS AND CORRELATIONS

Twenty-nine patients had elective postoperative cardiac catheterisation with angiography one to 12 years after operation; 11 had repeated studies. Ten patients had no investigations for reasons already given. Peak systolic gradients before and after operation, at the first postoperative study at rest, and with isoprenaline are shown (Fig. 14a and b) The height of the preoperative gradient could not be used to predict a positive response to isoprenaline (dynamic obstruction) after operation though it was more likely in those with gradients above 80 mmHg and unlikely in those with gradients of 60 mmHg or less (Fig. 14b).

There was no absolute correlation between the height of the gradient measured immediately after operation and the subsequent haemodynamic response. Those left with gradients above 25 to 45 mmHg at operation often had a positive dynamic obstruction at the first postoperative study. However, one patient with a resting gradient of 55 mmHg immediately after resection, which remained and rose to 90 mmHg with isoprenaline, showed regression of left ventricular hypertrophy from grade 4 to 1, and nine years later the patient had no resting gradient and only 50 mmHg after isoprenaline.

By contrast, those with absent or small gradients on the table after resection usually did not have dynamic obstruction, but there were two unexpected exceptions who developed worsening electrocardiograms and severe dynamic obstruction, one with symptoms.

Only one of the seven patients with a raised end-diastolic pressure in the left ventricle before operation had the capacity to develop severe outflow obstruction in the postoperative course. This was

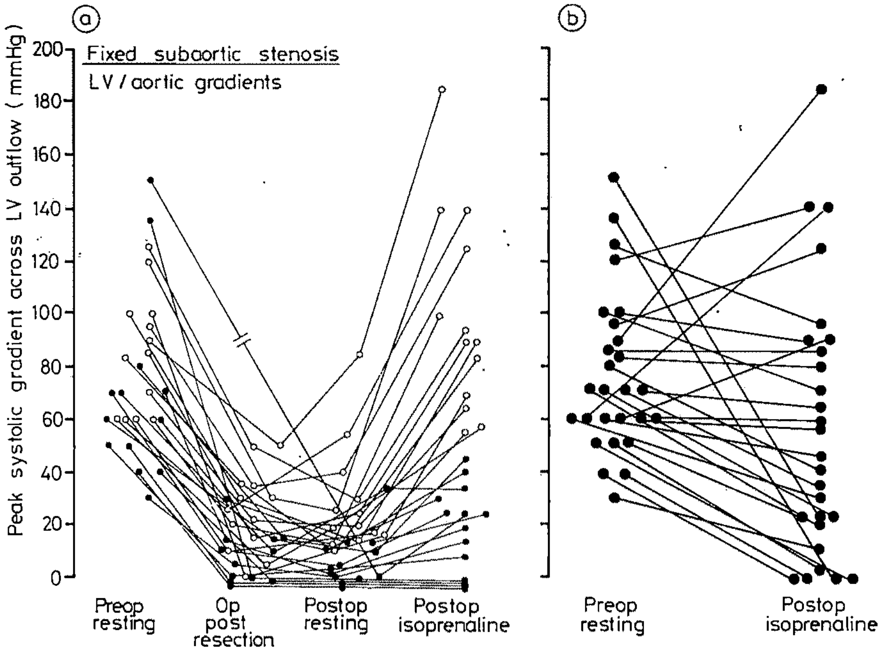


Fig. 14 *Peak systolic gradients across the left ventricular outflow tract before and after resection of a fixed subaortic stenosis.* (a) *Shows gradients at rest before operation, immediately after resection at surgery, resting at first postoperative catheter performed one to five years after the operation, and after isoprenaline stimulation. For clarity, open circles refer to patients whose gradients rose above 50 mmHg with isoprenaline after operation. Black circles refer to patients in whom isoprenaline produced gradients of less than 45 mmHg.* (b) *Peak systolic gradient before operation and gradient produced by isoprenaline after operation in individual patients.*

a 12-year-old girl who presented in failure with a duct.

The response of the left ventricular and aortic pressures after an ectopic beat was as seen in obstructive hypertrophic myopathy in the group with dynamic gradients but was normal in those with "myopathic" ventricles and in those with unimportant or absent outflow gradients. Angiography usually showed little change from the preoperative appearances of the left ventricular mass. The aortic valve appeared to open more normally but was usually still visible suggesting some thickening of the cusps. Angiographic assessment of postoperative fixed obstruction was even more difficult than before operation. The appearance of the left outflow tract was most normal and open in those with important aortic regurgitation and in two after total root and valve replacement with a "fresh" homograft.

Left ventricular function, as measured by ejection fractions and plotting the shortening curve, showed that the majority of patients had ejection fractions ranging between 65 and 82 per cent (H W M Plokker, personal observations). Three patients had a low ejection fraction ranging from 30 to 50 per cent, two of the three having been in heart failure before operation. None of these had a gradient above 25 mmHg nor a positive isoprenaline response.

Postoperative left ventricular angiography in 12 showed an abnormal looking left ventricle (like hypertrophic cardiomyopathy), either unchanged in comparison with preoperative appearance or worse (Fig. 15a and b). Three patients with gradients above 50 mmHg and a positive isoprenaline response, seven to 10 years after operation, had the appearance of "tunnel obstruction" (Fig. 9b) which had not been present before the initial procedure.

Discussion

Surgical removal of a fixed subaortic stenosis as a first procedure under direct vision had a low perioperative mortality and can be considered a safe procedure unless the patient was referred in a terminal state with an added complication, as exemplified by the one operative death in 40 patients. Careful inspection of the subvalvar region in any aortic valve replacement, particularly when the valve has been attacked by endocarditis and surgical attention is centred on that, is mandatory, and had this been done at the first operation death at the subsequent operation might have been prevented.

Problems after surgery may develop in relation to damage to the aortic valve, to the mitral valve, or to the conducting tissue which appears to be vulnerable in patients who have needed additional right ventriculotomy to close a ventricular septal

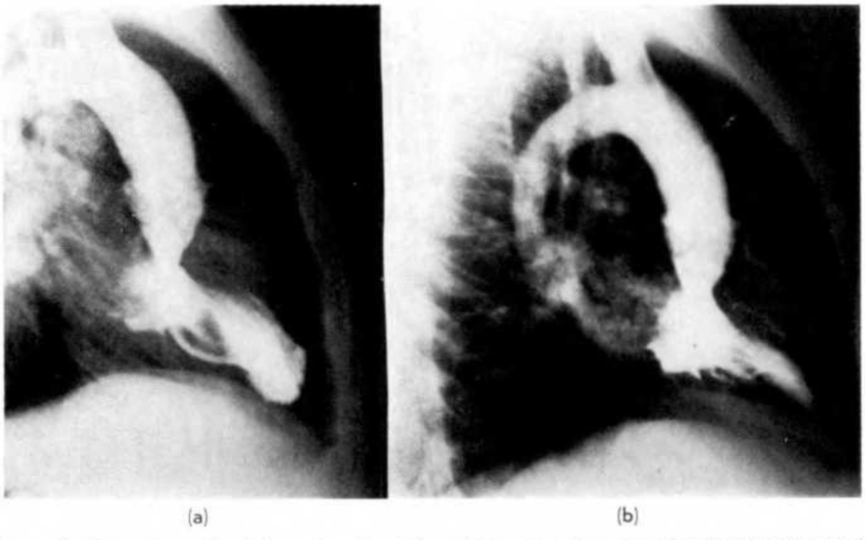

(a) (b)

Fig. 15 *Left ventricular angiography before operation* (a), *and one year after operation* (b) *showing persistence of abnormal muscle and some narrowing of the subaortic region. Immediately after resection the gradient was 5 mmHg and at first postoperative catheterisation it was 40 mmHg, rising to 80 mmHg with isoprenaline. Nine years later it was 50 mmHg, rising to 90 mmHg and he had breathlessness, with worsening oj the electrocardiogram and features of persistent dynamic obstruction relieved by propranolol. Redeveloped fixed obstruction is suspected.*

defect or resect infundibular stenosis. Our practice now is to warn relatives of patients with the dual problems that long-term pacing might be needed after operation. Even with stable rates of 40 to 50/min patients have symptoms, probably a result of the diffuse myocardial problem and for this as well as other sinister developments, permanent pacing is necessary once block has been established. It may also be needed if transient block has occurred.

Surgical trauma is not the only cause of complete heart block in patients with fixed subaortic stenosis. It may develop late, as in the eldest patient aged 57 years, from progressive myocardial fibrosis or associated coronary disease. Complete heart block in patients with discrete subaortic stenosis may also be acquired during endocarditis on the aortic valve from a burrowing infected aneurysm.[11]

Pathological and physiological abnormalities of the aortic valve are present in the majority of patients with surgically significant subaortic stenosis. Lesions may be congenital (22·5%) or more commonly are acquired with thickening from jet lesions which for life remain a site for infective endocarditis before and after operation. The incidence and severity of acquired changes on the aortic valve increase with age; this is one reason for removing fixed subaortic stenosis early after diagnosis.

Aortic regurgitation sometimes increases after removal of a subaortic stenosis if a cusp is damaged or after an over-zealous valvotomy. Those in whom aortic valve replacement has been needed will require further surgery. Mild aortic regurgitation is usually unchanged after careful removal of the subaortic obstruction; the regurgitant murmur may disappear. Those with a successful aortic valve replacement, completely relieving the valvar gradient, did not develop dynamic obstruction and seemed to do better in the long term.

The anterior cusp of the mitral valve may be damaged during the resection of the attached fibrous stricture. The papillary muscle may be aberrantly attached and contribute to new or worsening mitral regurgitation. Mitral regurgitation may also develop secondary to progressive or increasing left ventricular dysfunction. Whether this is related to intraoperative ischaemia, which was not prolonged in this series, or to natural progression of myocardial disease is uncertain.

Apart from these complications which occurred in 20 per cent, it might be assumed that once the fixed organic obstruction has been removed the patient's major problem is solved. This series shows that the problem is not so simple. Lambert *et al.*[12] in assessing a small group of patients after removal of fixed subaortic stenosis commented that their state was "unpredictable" and others have been faced with the need for reoperation and worsening electrocardiograms.[4 13]

Persistent dynamic obstruction with and without fixed obstruction occurred in 44 per cent of survivors. Another seven (18%) had features of congestive myopathy which appeared to be progressive in one who died; in the other death the left ventricular dysfunction may have been iatrogenic.

Clinical signs initially suggested the presence of dynamic obstruction in the postoperative patient who presented with jerky pulses with rapid upstroke, persistent long aortic systolic ejection murmur, and hyperdynamic left ventricular pulsation in the absence of obvious aortic regurgitation.

One is tempted to assume that the response produced by isoprenaline may also occur with emotional and other adrenergic stresses of daily life in such prone patients and that may be the cause of electrocardiographic variation and deterioration seen in some of the late postoperative patients. Similar dynamic responses occur sometimes after surgery for other forms of left ventricular obstruction such as aortic valve stenosis, supra-aortic stenosis, and occasionally coarctation of the aorta. Large areas of dysplastic myocardium in the septum, papillary muscles, and free wall of the left ventricle have been demonstrated in these and other congenital malformations.[14 15]

Such muscle presumably develops and behaves abnormally in the presence of fixed obstruction and remains behind after the obstruction is removed. Given the stimulus from increased work from residual obstruction, or possibly athleticism, as well as sympathomimetic drugs, such muscle may continue to function abnormally and even progress to cause symptoms. It is clear that the giving of isoprenaline support in the early postoperative period is undesirable unless the myocardium has been in failure or been insulted during the operation.

The finding of dynamic obstruction in the early years after apparently successful resection of a fixed subvalvar obstruction in more than 50 per cent of patients operated on under 20 years requires explanation and understanding. Its influence on long-term prognosis appears to be of importance from this series even though patients with it were well. Certainly, in the early years, there were no signs of symptoms or deterioration except in the one patient who clearly had residual fixed obstruction left at the first operation performed hastily after cardiac arrest and who required reoperation two years later.

The dynamic obstruction persisted in seven of the eight in whom it was initially demonstrated, and who had further studies four to 10 years later.

In only three was there a slight increase in the resting gradient whereas in the others it actually fell with time. Thus, it appears in the small group who have had repeated catheterisation that the presence of dynamic obstruction may predispose to development of progressive fixed obstruction or progressive dynamic obstruction. Neither course is predictable with certainty for there was one boy with a gradient on isoprenaline of 90 mmHg one year after operation and eight years later he had no gradient at rest, rising to only 50 mmHg with isprenaline and an electrocardiogram originally with grade 4 changes which regressed to grade 1. Perhaps it is relevant that he led an entirely sedentary life, refusing employment. Looking at the whole group with evidence of dynamic obstruction, nine are without symptoms but the electrocardiogram has deteriorated after improvement for two to four years in three, a further three developed angina or dyspnoea, and five have a reformed fixed subaortic ring or crescent. Only six had no long-term problems for four to seven years and so it appears that despite absence of symptoms and electrocardiographic improvement, these patients may still develop problems, with or without re-development of fixed obstruction. In the hope of preventing progressive muscular obstruction, propranolol in small doses is now given long-term to patients with dynamic obstruction. Large doses are not given as children and adolescents seem unusually sensitive, with falling off in concentration and school performance. Pregnancy is not contraindicated in these patients; five pregnancies were successfully completed and all of the patients had important dynamic obstruction. Presumably the volume overload was beneficial for the hypercontractile ventricle.

It could be argued that part of the dynamic gradients was sometimes created by trapping of the catheter tip which may be a problem in hypertrophic obstructive myopathy. Care was taken to try to avoid this and there were clinical features suggesting the presence of dynamic obstruction in those patients where it had been documented. The possibility that these were spurious gradients has therefore been ignored.

Not all patients with fixed subaortic stenosis show signs of dynamic obstruction after operation. Since it appears to be important in the postoperative evolution, retrospective assessment of preoperative data has been looked at to see who is "at risk". The anatomy of the fixed obstruction, whether ring or crescent, was not a predictor of the postoperative course, nor did it appear to matter whether the obstruction was all close to the aortic valve or lying obliquely and deeper. Age at the time of operation appeared to have some influence. Persistent dynamic obstruction was not seen in those below 8 years or those over 35 years. Younger patients may have had milder obstruction with less secondary effect on the myocardium; older patients perhaps had more fibrosis as was suggested by the more frequent "myopathic" response. Dynamic obstruction was most common in those operated on in the second decade which is when the majority presented. It was also more frequent, but not constant, when there was grade 4 left ventricular hypertrophy established and was never seen in those with left bundle-branch block before operation. The best indication that dynamic obstruction would persist was the morphology of the left ventricle on angiography and not the anatomy of the obstruction removed. Those with eccentric muscle lumps and excessive septal hypertrophy in systole (Fig. 3 and 15), that is some of the features described with "primary" hypertrophic cardiomyopathy including midventricular obstruction, always had postoperative dynamic obstruction. Those with concentric regular hypertrophy, even with grade 4 electrocardiographic left ventricular hypertrophy, did not develop it provided the fixed outflow obstruction was completely relieved at the initial operation.

Not only were there different angiographic appearances of the left ventricle but also the ascending aorta and root showed different forms. There were some who had no post-stenotic dilatation with small or normal sized aortic root and ring, often with slight supravalve narrowing; these were associated with eccentric muscle, persistence of dynamic obstruction, and reaccumulated fixed obstruction. Residual resting gradients were usually higher in this group. There were others with a normal or wide root and ring; these had more smooth concentric hypertrophy or even dilated ventricles. Such observations suggest that fixed subaortic stenosis may occur in two different pathological cardiovascular systems even though the haemodynamics and clinical presentation may be the same. We suspect that the first group may have serious diffuse congenital cardiovascular disease in which areas of extensive congenital dysplastic myocardium are present[14 15] with a small root and abnormal aorta, as occurs in variant forms of congenital aortic valve stenosis[16] and some types of supra-aortic stenosis,[17] and a milder more simple condition where the congenital disease is mainly localised to the subvalvar area. The latter are the ones with a better postoperative course.

Dysplastic muscle is commonly found in association with structural congenital cardiac anomalies. Whether it manifests clinically probably depends on the extent of myocardial involvement and the basic haemodynamic disturbance. Patients with distal outflow obstruction, either on the right or left side, and excess dysplasia are almost certainly the ones who may have clinical manifestations of added problems. We suspect that a high proportion of patients with fixed subaortic stenosis are in this category. It is thus important to remove the visible fixed part of the obstruction as completely as possible in such patients. The gradients recorded on the table were not constantly helpful and often gave the surgeon false security. If gradients on the table were over 30 mmHg dynamic obstruction and further fixed obstruction might develop but if they were 0 to 20 mmHg it could also happen. This presumably relates to the state of the myocardium, temporarily poisoned or ischaemic after the bypass; such measurements may be more meaningful, with techniques of better protection of the myocardium, or after the use of isoprenaline. Patients with significant aortic regurgitation, aortic valve replacement, and no, or small, resting gradients at the first study did not develop dynamic or progressive obstruction.

When fixed subaortic stenosis reaccumulated, it presented a difficult surgical problem since re-excision of the shelf or ring alone did not relieve the gradients. Good haemodynamic relief was achieved only after excision of the whole aortic root, ring, and cusps. When this was done, together with subvalvar muscle resection, the muscular outflow opened like a flower once the small ring was removed.[9] In three of these patients the root and valve were replaced by an adult fresh homograft into which the coronary arteries were reimplanted. Postoperative studies have confirmed complete abolition of the gradients, with a competent aortic valve. This procedure seems a more attractive and physiological answer to diffuse left ventricular outflow obstruction than the placing of an apical-abdominal aortic tube. The need for such extensive surgery for what was initially a comparatively simple lesion highlights the malignant aspects of fixed subaortic stenosis if the lesion is not treated early and completely as its continued presence in certain patients with congenital cardiovascular disease may predispose to the formation of "tunnel" obstruction.

Redevelopment of fixed subaortic obstruction is obviously related to several factors. The ability to reform the fixed subaortic stenosis which has the same histopathology as the first ring or shelf provides reason to speculate on the aetiology and pathogenesis of this lesion in the first place. It is possible that both the first, as well as the reformed ring or shelf, were acquired in postnatal life and not present at birth (congenital). Such a view is supported by the fact that no experienced cardiac pathologist has reported this lesion causing critical obstruction in the newborn or infant human heart.

Experimentally, in a special strain of Newfoundland dogs a fully developed fixed subaortic ring/crescent was only found in dogs over 3 months.[18] The puppies who died between the ages of 3 and 6 months showed the effects of endocarditis on the jet lesion of the aortic valve and not a severe obstructing lesion with secondary myocardial changes. In the only heart examined from a child under 2 months who was alleged to have died from fixed subaortic stenosis, personal inspection confirmed the presence of a fleshy shallow ridge just below the abnormal aortic valve, which did not cause serious obstruction with only a 1 to 2 mm protrusion. However, the heart had extreme thickening of the left ventricle and visible severe septal bulging, suggesting that the myocardium was abnormal and disproportionately abnormal in comparison to the mild fixed obstruction.

If it is accepted that the fixed subaortic stenosis removed by surgeons is acquired, there then occurs the problem of why it forms at all. That it forms in relation to some congenital abnormality of the outflow tract is likely, since 60 per cent of patients have other obvious congenital cardiovascular anomalies.

The pathological behaviour of the myocardium, including that with a "congestive" response, after operation for fixed subaortic stenosis in about 60 per cent raises the possibility that the primary abnormality is in the heart muscle and that this contracts abnormally causing turbulence in the outflow, with deposition of fibroelastic material which ultimately causes a fixed obstruction. Not only is there a clinical similarity in the behaviour of the left ventricle in the living patients with hypertrophic cardiomyopathy and some with fixed subaortic stenosis but also histological overlap as well as differences.[19 20] Though the myocardium in these patients may be abnormal at birth it is doubtful if it is the cause of fixed subaortic stenosis as there are 30 to 40 per cent of patients who show no such problems after resection of fixed subaortic stenosis. Histological study of the muscle biopsied from the ventricular septum has been of no help in predicting the outcome since the biopsies are usually reported to show non-specific fibrosis and hypertrophy, even when there is good evidence of dynamic obstruction and unusual muscle. Perhaps this is because the biopsies are too superficial and the real problem lies deep in the septum and elsewhere. Helpful evidence comes from examination of two hearts, provided by Dr Luis Becú, from children aged 9 and 15 months who died from lung infections, associated with a large duct. Trivial fixed subaortic stenoses were present in both; dysplasia, fibrosis, and hypertrophy were present in both but in neither was there enough dysplasia to consider that a primary myocardial abnormality was present.

One is therefore forced to search for some other primary (congenital) defect. In both hearts there was a minute non-obstructive fleshy ridge beneath the aortic valve cusp and the anterior mitral cusp at the site where the mature fixed subaortic stenoses are later found in some (Fig. 16). This is not the lesion found later and it resembled the fibrocartilagenous lump in the Newfoundland puppies.[18 21] Perhaps this ridge is the remnant of some embryonic fold and is the basic congenital abnormality causing turbulence and the development of the mature fixed fibroelastic subaortic stenosis which the surgeon removes later. Such a course would be encouraged by the excess turbulence caused by the increased flow by a duct or ventricular septal defect present in many patients with fixed subaortic stenosis. This fleshy ridge is not seen at operation nor in necropsy specimens from teenagers and adults who die with this disease, and is perhaps absorbed or sculptured out in natural changes in postnatal cardiac morphology. It could be argued that these hearts might never have developed fixed subaortic stenosis had the patients survived. We think it is likely they would and suspect that the little lump is the one congenital defect responsible for the development of the fully formed fixed subaortic stenosis which the surgeon removes many years later. If obstruction within the left ventricular outflow tract remains, turbulence persists and the same fibroelastic shelf or ring may form. The recent intriguing work of Rosenquist and his colleagues[8] shows muscle bands causing increased separation between the aortic and mitral cusps in patients with fixed subaortic stenosis which may provide the missing link about the primary congenital abnormality.

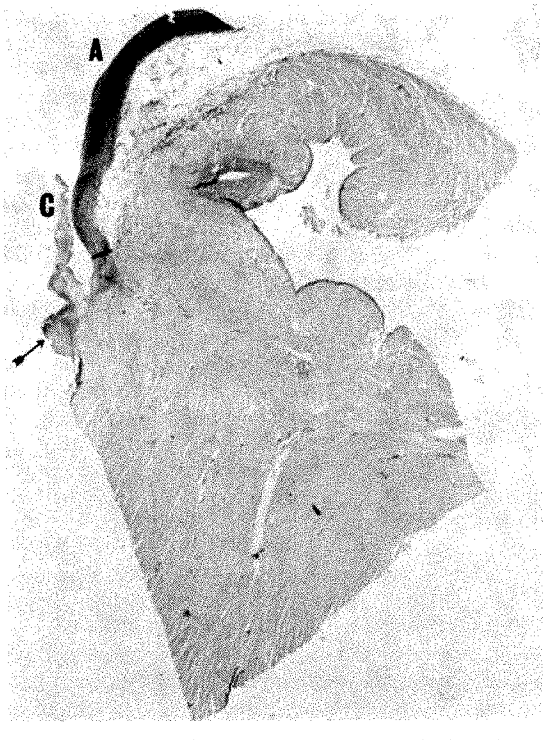


Fig. 16 *Cross-section of heart from 9-month-old child with duct who died from overwhelming infection. This shows a minute subaortic ridge* (arrow), *not causing any important obstruction, beneath a normal aortic valve cusp (C). The ascending aorta (A) is normal.*

Whatever the pathogenesis of subaortic stenosis or the cause of the abnormal muscle response, current policy is to remove fixed subaortic stenosis as soon as it is recognised, even with low gradients, that is below 30 mmHg, and not wait for secondary changes, or for symptoms, or for any electrocardiographic changes. The need to differentiate such patients from mild aortic valve stenosis is obvious since those with mild to moderate aortic valve stenosis should not have premature surgery as it may interrupt growth of the root or cause serious incompetence of the valve. Because of the difference in management any patient suspected of having fixed subaortic stenosis should be investigated with angiography early. Early experience suggests that the two-dimensional echo is reliable in recognising developed fixed subaortic stenosis, whereas the M-mode is not always, particularly in mild lesions. Furthermore, persistence of a long ejection systolic murmur in patients after duct ligation demands early investigation.

From careful evaluation of this group of patients late after resection of subaortic stenosis we conclude that results may not be as good as initial assessment suggests. The left ventricle may continue to behave abnormally either hypercontractile like hypertrophic myopathy, or "congestive" features and changes may advance. Patients need careful supervision, good early routine postoperative haemodynamic evaluation, and protection from infective endocarditis for life. Their problems are not completely cured and some may persist or even return mysteriously.

We thank Mr Keith Ross for permission to include the 10 patients on whom he operated in the National Heart Hospital. We are particularly grateful to

Dr Luis Becú for providing information on the histology of fixed subaortic stenosis and two hearts for examination. We are indebted to Dr A Rickards who provided routine haemodynamic data and encouraged the extensive evaluation of left ventricular function, and to Dr Simon Rees and the late Dr Keith Jefferson for radiological evaluation.

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Br Heart J 1980; **43**: 648–60

Pathogenetic mechanisms of angina pectoris: expanding views*

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It was with pride that I accepted the honour of giving the Thomas Lewis Lecture for 1977 and I have chosen to present a subject to which we have devoted our main research efforts during the past 10 years. This Memorial Lecture seems to me an appropriate occasion to present our findings, because they represent the fruit of investigations performed in the scientific spirit of Sir Thomas and because they bring objective support to an hypothesis that he had brilliantly anticipated over 40 years ago,[1] on the basis of acute clinical observations and of logical deductions.

In the first part of my presentation I wish to outline the considerations that inspired our studies, in the second I will illustrate our results, and in the third I will put forward the implications of our expanding views on angina pectoris.

Traditional hypothesis

It is generally accepted that angina pectoris is caused by a transient, acute imbalance between myocardial demand and coronary blood supply. This imbalance is traditionally ascribed to coronary artery stenosis which sets a fixed limit to the possible increase in myocardial blood flow so that angina ensues whenever oxygen supply falls short of myocardial metabolic demand. This has been proven repeatedly to be a possible mechanism of angina pectoris, and as a result a rather restrictive definition of angina pectoris has gained acceptance. Thus, Friedberg[2] writes: "... the occurrence of the pain or pressure with effort is an essential element of the syndrome although it does not occur invariably with the same exertion. The pain of angina pectoris may occur at rest, but if it does not also occur with effort or cannot be reproduced by bodily exertion the diagnosis of angina pectoris may be questioned." Thus, though he recognised that angina might occur with variable levels of exertion and even at rest: (1) he implicitly attributed the variable threshold of angina only to different levels of myocardial demand for the same work; and (2) he practically denied the existence of angina at rest with unimpaired exercise tolerance and the possible role of a functional variability of myocardial blood supply. By extrapolation, this opinion helped to generate the notion that the only variable capable of determining a transient acute imbalance between myocardial demand and supply (and thus produce myocardial ischaemia) was an excessive increase in myocardial demand relative to the fixed limitation of supply caused by coronary atherosclerosis. The conclusions of the editorial by James[3] that "the most frequent explanation for angina without coronary disease is an incorrect interpretation of the coronary arteriogram" is a clear expression of a concept so deeply ingrained that it was difficult to recognise that it was actually a hidden assumption. In fact, the demonstration of stenosis of a coronary artery cannot be considered, *per se,* as proof that attacks of angina result from an increase in myocardial demand beyond supply; it is also necessary to show that they occur because local coronary flow reserve is exceeded.

Conflicting findings

Several observations contradict the traditional hypothesis that the only mechanism of angina is an excessive increase in myocardial demand in the presence of critical coronary stenosis and suggest that the relation between coronary atherosclerosis and clinical manifestation of the disease is a direct one.[4]

(1) A review of the published reports discloses that about 10 per cent of patients with angina have normal coronary arteries or no critical lesions.[5] Furthermore, about 10 per cent of patients with "unstable angina" and typical electrocardiographic changes had to be excluded from randomised surgical trials because they were free from significant coronary stenosis.[6 7]

(2) In patients with angina no reasonable

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* Thomas Lewis Lecture, London, 24 November 1977

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Received for publication 9 January 1979

prediction of the extent of the coronary stenosis can be made on the basis of the severity of symptoms.[8-14] Furthermore, the extent of coronary atherosclerosis in patients with unstable angina is similar to that of patients with stable angina.[15 16]

(3) An appreciable number of subjects with documented severe coronary atherosclerosis have a normal effort electrocardiogram despite full exercise stressing.[14 17] These reports are consistent with the findings at necropsy of severe coronary atherosclerosis in a considerable number of asymptomatic persons dying of non-cardiac causes.[18-20] Furthermore, the presence or absence of clinical symptoms cannot be related to the variable development of collaterals, these collaterals being related only to the degree of coronary stenoses.[20] Thus, the comparison of the high incidence of coronary atherosclerosis in the general population with the relatively low incidence of ischaemic heart disease suggests that the presence of stenoses, *per se,* cannot be considered as the only determinant of the clinical manifestations of the disease.[21]

(4) Animal experiments indicate that: (a) in the presence of an acute reduction of the lumen of a major coronary branch by 65 per cent, flow across the stenosis can still increase by about five times the resting level[22]; (b) only in the presence of a 90 to 95 per cent acute lumen reduction does flow through the stenosed branch decrease below resting level[22]; (c) normal myocardial flow distribution was observed in dogs during submaximal treadmill exercise six months after ameroid closure of the left circumflex artery.[23] Thus, functional factors interfering with the relation between myocardial demand and supply, in the presence or absence of coronary atherosclerotic stenosis, must play a role in the genesis of angina pectoris. Similar conclusions were reached by Lewis[1] in relation to attacks of angina at rest. On the basis of careful measurements of heart rate and blood pressure in patients during successive attacks of angina at rest and during physical exertion, Lewis concluded: "It appears almost necessary to assume that a strict relation between pain and pressure is broken by some factors of interference and the factor in mind is an inconstant state of the coronary vessels". However, the hypothesis of coronary vasoconstriction, considered as a cause of angina pectoris long ago by Latham,[24] and Osler,[25] and other distinguished authors, fell into disrepute when nearly all patients with angina were proved at necropsy to have coronary artery atherosclerotic obstructions of variable severity.[26] Because pathologists could document so clearly the atherosclerotic stenosis but were unable to obtain any evidence of vasomotor tone during life in their necropsy specimens, they felt entitled to deny categorically the existence of other mechanisms that they could not objectively demonstrate.

The hypothesis of coronary vasospasm was proposed by Prinzmetal *et al.* in 1959[27] to account for the form of angina that he described as "variant" and which has stimulated more recent research using recent advances in technology.

Studies of angina at rest

Following this line of reasoning, we have concentrated our interest on the study of angina at rest where, according to clinical experience, functional factors might be expected to play a major role.

Typical transient electrocardiographic abnormalities (ST segment depression or elevation greater than 0·2 mV) were documented during at least one spontaneous attack of angina in 193 patients admitted to our institution between 1970 and 1977 with attacks of angina at rest.* In these patients, clinical histories, electrocardiographic changes during angina, and coronary arteriographic findings were extremely variable. The onset of angina ranged from 25 years to a few days before admission to hospital. More than a third had had a previous myocardial infarction and more than two-thirds also gave a history of exertional angina which sometimes preceded, but more often followed, the onset of angina at rest. A minority reported such severe limitation of exercise tolerance that they were consistently prevented from climbing a single flight of stairs or from walking 100 metres at a slow pace.

These patients were the subject of our research, which has developed along five lines.

CONTINUOUS ELECTROCARDIOGRAPHIC MONITORING

With the aim of investigating the pattern of transient electrocardiographic changes and their relation to anginal pain, and to arrhythmias, we recorded over 7000 electrocardiograms during transient ischaemic episodes with or without pain.[28]

The most striking observations made possible by the large number of episodes of transient myocardial ischaemia recorded were:

(1) the great variability of the transient electrocardiographic changes in different patients and in the same patient during different episodes and during successive phases of the same episode;

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* Patients with typical angina at rest, with or without old myocardial infarction, who did not show typical electrocardiographic changes during their spontaneous attacks of angina, were not included in this group.

(2) the delayed appearance of pain relative to the onset of electrocardiographic changes;

(3) the frequency in some patients of typical, transient ST segment and T wave changes, similar to those observed during attacks of angina, which were not accompanied by chest pain, and of T wave changes alone with or without pain.

In those patients in whom unequivocal electrocardiographic changes were documented at least once during angina, elevation of the ST segment (of at least 0·2 mV) in at least one lead, with or without depression in other leads, was more frequent than depression. However, while some patients consistently showed ST segment elevation in the same leads in all episodes, others frequently or occasionally presented with episodes characterised by ST segment depression and/or transitional forms such as peaking of T waves, negative T waves becoming upright, or inversion of positive or flat T waves. Conversely, other patients who usually showed ST segment depression, occasionally showed transient reversible ST segment elevation and/or transitional forms. All these changes were observed with or without anginal pain.

These observations show that (a) elevation of the ST segment, described by Penati,[29] Brow and Holman,[30] Secondari,[31] and Wilson and Johnston[32] and considered to be the hallmark of the variant form of angina by Prinzmetal,[27] appears to be simply the most dramatic aspect of a continuous spectrum of electrocardiographic changes during angina rather than characteristic of a well-defined syndrome[28]; and (b) anginal pain is not a sensitive index of the presence of acute transient myocardial ischaemia because it occurs late and it may be absent.

STRESS TESTING

Because of the frequent absence of a history of progressive decrease of exercise tolerance to minimal levels, we considered it of great practical relevance to study the coronary flow reserve of these patients. We therefore performed sitting bicycle ergometer exercise stress testing, with continuous supervised monitoring of the electrocardiogram, and of the blood pressure in most patients (initially only in a few and recently in all). More recently, we have studied a group of patients by comparing the values of the heart rate systolic blood pressure product (as an index of myocardial oxygen demand) measured at the onset of the ischaemic episode at rest with that attained at the angina threshold during pacing-induced tachycardia. These studies showed the following:

(1) The coronary flow reserve of these patients was usually not reduced to the extremely low levels expected from their history: angina never developed below an exercise level of 50 watts for two minutes and only very few patients developed ST segment depression at 25 watts; most patients could perform up to 75 or 100 watts and several had a negative stress test.[28 33]

(2) The heart rate systolic blood pressure product at the onset of the spontaneous attacks of angina was consistently much lower than that attained at the angina threshold during atrial pacing or exercise.[34]

These observations show that: (a) it is illogical to assume without proof that spontaneous attacks of angina at rest result from an increase in myocardial oxygen demand in excess of that tolerated during the stress test; and (b) two different causes of angina should be postulated to coexist in patients with angina occurring at rest at a much lower level of cardiac work than that causing exertional angina.

CONTINUOUS HAEMODYNAMIC MONITORING

For rational management of these patients we considered it essential to show whether or not the attacks of angina at rest were caused by an increase in the haemodynamic indices which determine myocardial oxygen demand. Thus, in collaboration with Drs Chierchia, Marchesi, Pesola, and Mimmo, we continuously monitored arterial and intracardiac pressures for several hours in patients with frequently recurring attacks of angina. These studies[35 36] showed the following:

(1) There was no significant increase in heart rate, systolic blood pressure, or left ventricular contractility (as indicated by left ventricular peak dP/dt) preceding the onset of the ST segment changes, irrespective of their direction (Fig. 1).

(2) An impairment of ventricular function occurred during angina (sometimes with increases in left ventricular end-diastolic pressure up to 50 mmHg); the episodes with a more abrupt onset of ST segment change (usually elevation) were associated with a sequence of haemodynamic changes remarkably similar to those observed in the dog[37] after sudden coronary ligation (reduction of peak ventricular relaxation and contraction dP/dt, increase in end-diastolic pressure, drop in systolic pressure, and elevation of the ST segment) (Fig. 1).

(3) Pain consistently followed (sometimes by several minutes) the onset of the ST segment change; heart rate and blood pressure were sometimes increased at the onset of pain and increased further thereafter.

(4) A large number of transient episodes of typical ST segment elevation or depression, not

accompanied by pain, and of episodes of transient T wave change (peaking, inversion, inverted becoming upright) with and without pain, were recorded, and were associated with impairment of left ventricular function, similar to that occurring during episodes of typical ST segment elevation or depression with pain (Fig. 1).

These observations show that: (a) attacks of angina at rest are not caused by an excessive increase in myocardial demand; this is in contrast to the conclusion reached from studies based on isolated measurements at the onset of the attack of angina.[38–40] This contradiction may be related partly to the erroneous assumption that the onset of pain corresponds to the onset of ischaemia and partly to the assumption that the observation of an increase in heart rate and blood pressure was, by itself, sufficient proof that the coronary flow reserve was indeed exceeded. (b) Asymptomatic ST segment changes and atypical T wave changes may be an expression of acute myocardial ischaemia associated with obvious ventricular functional impairment and sometimes also with dangerous arrhythmia. Thus, pain and ST segment changes can no longer be considered the only hallmarks of acute myocardial ischaemia.

REGIONAL MYOCARDIAL PERFUSION STUDIES

Following our previous studies we decided to investigate whether these attacks of angina at rest were caused by a sudden transient reduction of regional myocardial perfusion. In collaboration with Drs Padodi, Severi, and Uthurralt, we performed thallium-201 scintigraphic studies during attacks of angina at rest in a large number of patients with a variety of transient electrocardiographic changes, with or without pain.

A regional reduction of myocardial perfusion was consistently documented regardless of the direction of the ST segment or T wave change and of the presence or absence of pain. Regional reduction of myocardial perfusion was massive and transmural during episodes characterised by elevation of the ST segment, and corresponded well with the leads involved by ST segment elevation,[41] but similar massive deficits of tracer uptake were also seen in patients with only transient ST segment shifts towards normal or peaking of T waves, with or

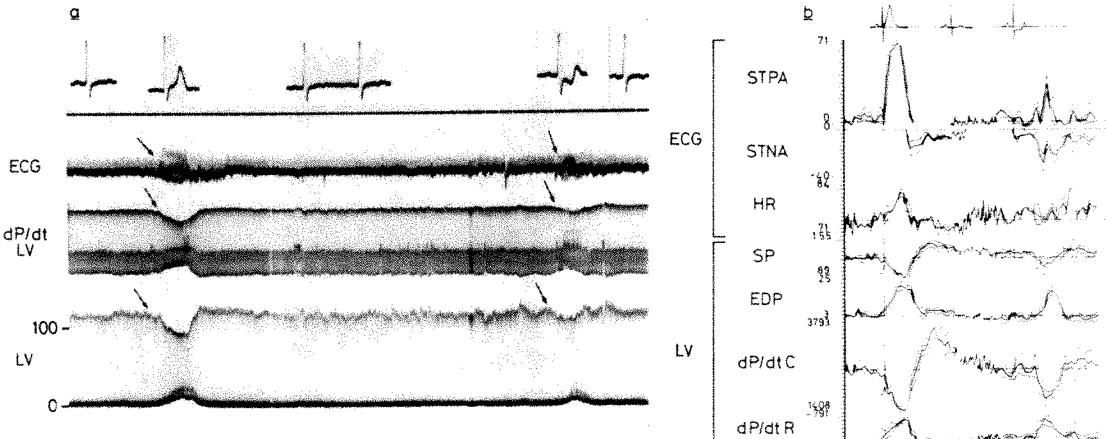


Fig. 1 *Transient episodes of acute myocardial ischaemia with ST segment elevation and depression may occur in the same leads within a few minutes, without symptoms. Continuous haemodynamic recording (in a patient who had episodes of angina with ST segment elevation and episodes with ST depression)* (a) *and computer analysis* (b). *During the recording, the patient had several episodes of angina with variable electrocardiographic changes; some electrocardiographic changes were asymptomatic. This recording shows two successive asymptomatic episodes characterised by haemodynamic changes similar to those observed during symptomatic episodes. In* (a), *the onset of the changes is indicated by arrows. In* (b), *the onset of the episodes of ST segment elevation and depression* (vertical lines) *is not preceded by any increase in heart rate, systolic blood pressure, or contractility. The presence of these electrocardiographic abnormalities is associated with impairment of dP/dt, and with increase in diastolic and reduction in systolic pressure of the left ventricle. STPA and STNA, positive and negative area of the ST segment of the electrocardiogram; HR, heart rate; dP/dt C and R, peak contraction and relaxation dP/dt.*

without angina. Less massive, more diffuse deficits of thallium-201 uptake were observed during episodes characterised by ST segment depression, a pattern compatible with diffuse subendocardial ischaemia.[42 43] Patients with attacks of angina with ST segment depression, occurring either spontaneously at rest or during an effort test, showed much more obvious deficits of thallium uptake during spontaneous than during exercise-induced attacks (Fig. 2), indicating a reduction of regional myocardial perfusion during spontaneous angina and an inadequate increase during exertional angina.[44]

More recently, Chierchia *et al.*,[45] in a study based on continuous monitoring of coronary sinus oxygen saturation, showed that transient ST segment changes and transient T wave changes, with or without pain, were not only accompanied by a reduction in regional myocardial perfusion, as shown by thallium-201 studies, but were also preceded by a sudden regional reduction of coronary blood flow.

From these observations it follows that: (a) the acute imbalance responsible for the attacks of angina at rest is caused by a sudden transient reduction of regional coronary blood supply rather than by an excessive increase in myocardial metabolic demand; and (b) a massive, transmural reduction of flow seems to result in ST segment elevation, inverted T waves becoming positive, or peaking of T waves; a non-transmural reduction of flow seems to result in depression of the ST segment or in T wave inversion, irrespective of the occurrence of pain.

CORONARY ARTERIOGRAPHY

Stimulated by the hypothesis of Latham,[24] Osler,[25] and Prinzmetal *et al*[27] and isolated fortuitous angiographic observations,[46–49] we began a systematic investigation of the possible role of coronary vasospasm in angina at rest. Thus, in collaboration with Drs L'Abbate, Pesola, Marzilli, and Ballestra, we obtained repeated selective coronary arteriograms during attacks of angina either spontaneous or induced by the intravenous injection of ergometrine, with the aim of demonstrating the occurrence of coronary vasospasm and of determining its site and its relation to coronary atherosclerotic stenosis and to transient electrocardiographic changes.

In the absence of symptoms or electrocardiographic signs of acute myocardial ischaemia, coronary arteriograms (obtained in about 80% of these patients) showed normal vessels or no critical stenoses in about 10 per cent, triple vessel disease in about 30 per cent, and one or two vessel disease in the remainder.[28] Severe coronary stenoses were found more often in those patients who also gave a history of exertional angina.

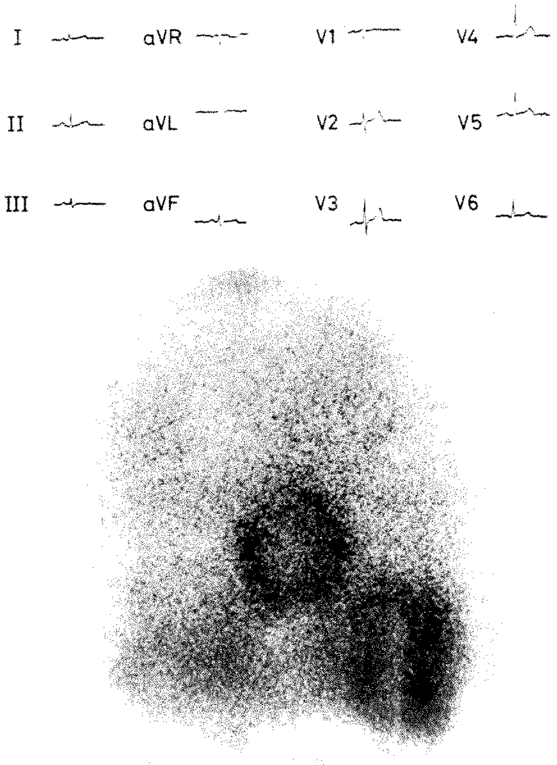
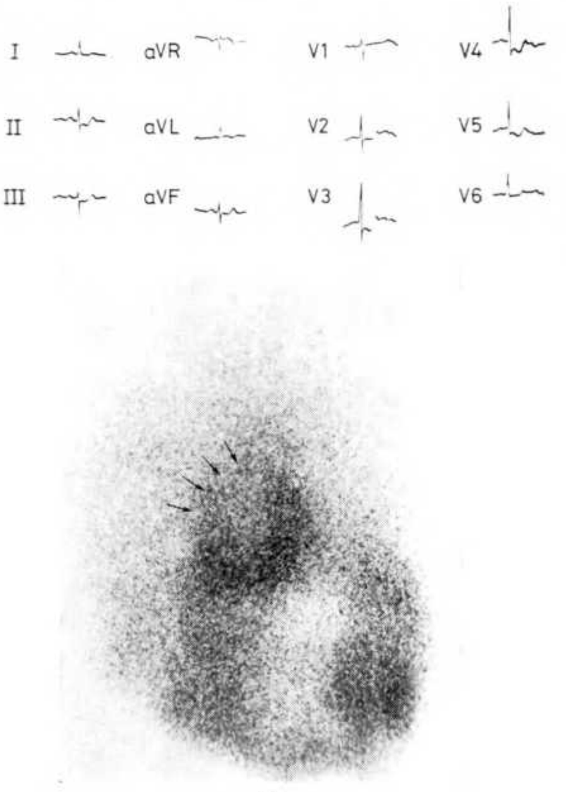


Fig. 2 *Regional myocardial perfusion is more severely impaired during spontaneous angina at rest than during exertional angina. Thallium-201 myocardial scintigraphy in left anterior oblique position, with 12 lead electrocardiogram* (top) *in control conditions* (a), *during spontaneous attack of angina at rest* (b), *and during angina occurring during exercise stress test at 100 watts/minute for three minutes* (c). *A deficit of perfusion is clearly visible in* (b) (arrows), *but is barely visible in panel* (c), *notwithstanding the similarity of the clinical symptoms and of the ST segment changes. We interpret this difference as meaning an actual flow reduction during angina at rest and to an inadequate increase during exertional angina.*

When contrast injections were made during an episode of transient ST segment change, with or without pain, transient vasospasm was observed in each case.[28 50–53] The severity and extent of spasm, the electrocardiographic abnormalities, and the degree of atherosclerosis in the vessel showing spasm were variable. Variable severity and extent



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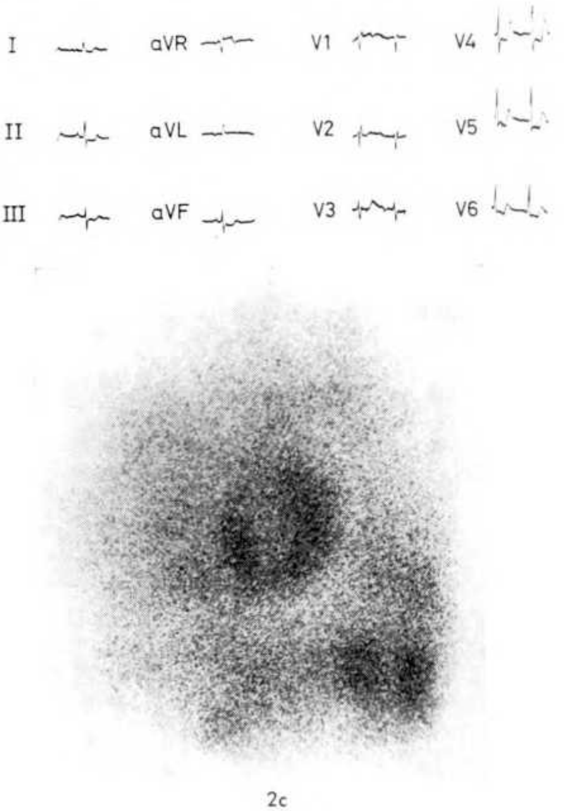

2c

of spasm was seen not only in different phases of the ischaemic episode, but also in successive episodes. Giant ST segment elevation was always associated with occlusive spasm of a main branch (main right, left anterior descending, circumflex) without distal filling, but similar angiographic appearances were associated also with lesser degrees of ST segment elevation, with peaking of T waves, and with negative T waves becoming upright (Fig. 3). In other instances these less-dramatic electrocardiographic abnormalities were associated with subocclusive spasm, with poor distal filling, sometimes retrograde via collaterals, and slow run-off. Often diffuse constriction of a branch coronary artery, noticed at the very beginning of an episode when there was only peaking of T waves, was followed by complete occlusion during obvious elevation of the ST segment.[28 51]

Typical widespread ST segment depression was associated with diffuse but less severe spasm of many branches, or with occlusive or subocclusive spasm of a large branch with severe atherosclerotic stenosis and some distal filling via collaterals. Conversely, isolated spasm of a diagonal or of a septal branch was observed in patients with isolated ST segment depression in the anteroseptal or anterior leads.[28 51 52]

Vasospasm was observed in vessels which were normal on angiograms, or which had wall irregularities only, or stenosis varying from 50 per cent to subocclusive.

Usually the vasospasm appeared to extend proximally and, when visible, also distally from the stenosis. Retrograde filling via collaterals of the vessel occluded by spasm was observed during some ischaemic episodes. Recently we failed to detect obvious spasm during spontaneous anginal attacks in one patient with severe coronary atherosclerosis; it is possible that a minor reduction in calibre, not easily detectable, may be sufficient to reduce the flow in these cases or that other mechanisms are responsible for the attack.

These observations indicate that:

(a) coronary vasospasm is responsible in the great majority of cases for the sudden reduction of myocardial blood supply documented by the flow studies;

(b) the vasospasm may involve vessels with any degree of coronary atherosclerosis. While patients with insignificant organic coronary artery stenosis have an unimpaired exercise tolerance, those with severe stenoses may also develop acute myocardial ischaemia when myocardial demand is increased beyond the coronary flow reserve. Thus, in some patients vasospastic angina may coexist with classical exertional angina; and

(c) the more frequent documentation of spasm during episodes of ST segment elevation can be attributed to the more dramatic changes in calibre of the main branches associated with this electrocardiographic pattern. In vessels with critically narrowed lumen, a small increase in vasomotor tone, not easily detectable angiographically, may be sufficient to reduce flow. In other cases constriction of resistance vessels may be responsible for the reduction in flow.

A distinction between spasm of large branches, increase in normal vasomotor tone, and constriction of resistance vessels may be relevant, because if different mechanisms are responsible, different specific treatments may be required. Platelet aggregation or other mechanisms cannot be assessed angiographically.

Perspective

Each of our five lines of research has yielded results which are in agreement with those of other similar studies.[54] These confirm the variability of the electrocardiographic changes,[55] the reasonably good coronary flow reserve,[56] the absence of increased myocardial demand,[57–59] the reduction in regional myocardial perfusion,[60–62] and the presence of coronary vasospasm during ST segment elevation[63] and depression.[59 64] The greater number of reports of angiographic demonstration of spasm during

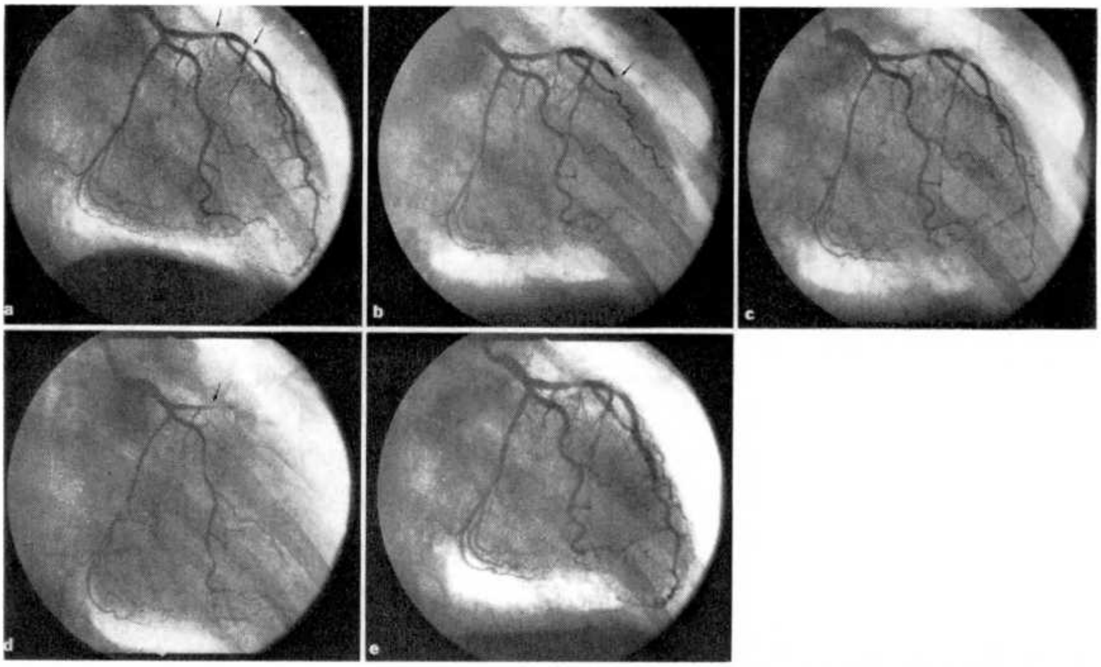

Fig. 3 *Coronary spasm may involve different parts of an artery and result in different electrocardiographic changes. The left coronary angiogram in the absence of symptoms shows two stenoses* (arrows) *in the left anterior descending (LAD)* (a). *The patient also had angina during severe exertion; the triangular electrocardiographic stress test became positive only at 150 watts every two minutes (workload increased every two minutes during continuous exercise without intermission), but he also had recurrent attacks of angina at rest with variable ST segment changes. Angiography during asymptomatic T wave elevation in V4* (b) *showed occlusive spasm in the middle third of the LAD* (arrow) *which disappeared spontaneously within a few minutes* (c); *about five minutes later he had spontaneous ST segment elevation with pain and showed occlusive spasm of the proximal LAD* (d, arrow) *which disappeared after intracoronary isosorbide dinitrate (0·2 mg) which caused evident coronary dilatation* (b).

episodes of ST segment elevation is probably attributable to the particular interest in this electrocardiographic pattern stimulated by the hypothesis of Prinzmetal *et al.*,[27] and to the more dramatic changes in calibre of the main coronary branches usually associated with this electrocardiographic pattern.

The results of these five lines of research fit together, like tesserae of a mosaic, to provide a clearer picture of angina pectoris. Therefore, I believe that the time has come to attempt a redefinition and a pathogenetic classification of angina pectoris which is both clinically useful and a stimulus to research.

REDEFINITION OF ANGINA PECTORIS

In the context of ischaemic heart disease angina pectoris appears to represent only a clinical syndrome, one of the possible manifestations of acute transient myocardial ischaemia, which may be completely asymptomatic, or may be accompanied by dyspnoea only or by rhythm disturbances only: it can result from various pathogenetic mechanisms and can be associated with various electrocardiographic changes. Anginal pain does not even seem necessarily to indicate a greater severity of ischaemia or risk of dangerous arrhythmias. Therefore, since management of angina has hitherto been inspired by the traditional concept of excessive increase of metabolic demand and since our studies have shown that this is not the only cause, a provisional updating of the classification of angina should help in the practical management of the patient.

CLASSIFICATION OF ANGINA PECTORIS

The clinical classification into "stable" and "unstable" angina has a prognostic significance only and serves as a guide to how carefully and intensively the patient should be managed rather than what type of management he should receive. I would like to propose the following provisional pathogenetic classification: angina "secondary" to increased myocardial demands beyond the fixed possibility of supply limited by coronary atherosclerotic stenosis (according to the now prevailing theory) and "primary" angina,* caused by other mechanisms.[65] This distinction should simply serve the purpose of an immediate clear-cut separation of the traditionally accepted mechanism of "secondary" angina, for which the diagnostic and therapeutic approaches are already reasonably well defined, from all other causes which require appropriate and specific management. As in the case of systemic hypertension, the pathogenetic classification will become more precise as the causes of "primary" angina become identified.

For practical management, patients should be classified as having (1) only "primary" angina; (2) only "secondary" angina; (3) predominantly "primary" or predominantly "secondary" angina (with or without transient electrocardiographic changes and with or without associated episodes of asymptomatic transient myocardial ischaemia). The mechanisms of "primary" angina and the degree of limitation of exercise tolerance in "secondary" angina (as a measure of the degree of limitation of the coronary flow reserve) should also be specified (Table).

For "primary" angina the only reasonably well-documented cause so far is coronary vasospasm, possibly because it has been more carefully sought than other postulated causes such as platelet aggregation,[66] small vessel disease,[67] transient myocardial metabolic abnormalities,[68] and inadequate vasodilatation.[69]

Table *Classification of angina pectoris**

Pathogenetic mechanisms	*Severity*
1) "Primary" angina — Vasospastic — ? — ?	Depends on: number and duration of the attacks, incidence of severe arrhythmias
(2) "Secondary" angina	*Grade 1:* angina occurs consistently and only during severe exertion *Grade 2:* angina occurs consistently during moderate exertion (fast walk for half a mile, climbing rapidly several flights of stairs); higher levels of work are never tolerated; lesser exertion never causes angina under ordinary conditions *Grade 3:* angina occurs consistently during lesser exertion (walking 100 yards, climbing one or two flights of stairs); higher levels of work are never tolerated; lower levels of exertion never cause angina under ordinary conditions *Grade 4:* angina occurs consistently with the slightest physical exertion (walking a corridor); higher levels of activity are never tolerated; angina may also be caused by increased heart activity at rest
(3) Mixed forms — predominantly "primary" — balanced — predominantly "secondary"	Combined criteria of "primary" and of "secondary" angina; patients who have a widely variable threshold of exertional angina or have *also* spontaneous attacks (not provoked by obvious haemodynamic changes) should be suspected of having mixed forms

* Patients may have variable electrocardiographic changes during angina and may also have asymptomatic episodes of transient acute myocardial ischaemia.

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* "Primary" is a term borrowed from other fields of medicine meant only to indicate our present ignorance about pathogenesis. It is expressly used to emphasise that this differentiation, rather than the proof of the existence of spasm, is the most important message of our expanding views on the mechanisms of angina pectoris. It is meant to stimulate an open-minded approach to any possible cause of angina.

In "secondary" angina, the severity of impairment of coronary flow reserve should be evaluated from a careful history and from the level of cardiac work at which the electrocardiographic stress test is consistently positive; the level of exertion that the patient can never exceed without the occurrence of symptoms or signs of acute myocardial ischaemia should be used to classify patients. The diagnosis of "secondary" angina should be confirmed by the demonstration of the presence of critical coronary stenoses.

With careful evaluation, the vast majority of patients we see fall into the third category and the minority into the second category listed in the Table.

RESEARCH APPROACH

New practical objective criteria for the diagnosis of transient acute myocardial ischaemia are needed. In fact, the low sensitivity of the traditional hallmarks of acute transient myocardial ischaemia, namely pain and ST segment changes, suggests a reconsideration of our set of equations: pain + ST segment changes = ischaemia; pain + atypical electrocardiographic changes, or ST segment changes − angina = uncertain; atypical ST segment changes − pain = no ischaemia.

It is inappropriate to discuss the "sensitivity" and "specificity" of electrocardiographic stress testing or of myocardial perfusion studies in predicting the presence or absence of coronary atherosclerotic lesions, because these tests are sensitive to ischaemia, which is not necessarily related to the presence of significant organic coronary lesions. In particular, these tests will not detect severe organic lesions if the latter are unaccompanied by ischaemia and, conversely, they will be positive in the presence of ischaemia even in the absence of significant organic coronary lesions.

The objective demonstration of the existence of vasospastic ischaemia should stimulate similar extensive studies for other possible pathogenetic mechanisms.

The prevalence of symptomatic and asymptomatic vasospastic acute myocardial ischaemia in ischaemic heart disease, its natural history,[28 70–72] and its role in the genesis of acute myocardial infarction and sudden coronary death,[28 72] should be investigated.

The identification of the causes of vasospasm, still largely controversial,[41 73–76] and of the factors that control the reversibility or irreversibility of vasospasm, is required for rational treatment and prevention. Meanwhile, the efficacy of symptomatic treatment in reducing or preventing angina attacks in patients with "primary" angina should be evaluated by means of repeated cross-over trials in individual patients,[77 78] rather than the usual double-blind studies in groups of patients, because of the possible individual differences in the aetiology of the disease and because spontaneous waxing and waning of symptoms often occur in these patients.

CLINICAL APPROACH

A careful history, continuous electrocardiographic monitoring, and electrocardiographic stress testing are at present the most valuable practical methods for the diagnosis of acute transient myocardial ischaemia. In those patients in whom a positive diagnosis can be made, the observation of whether angina occurs at a fixed or a variable threshold of cardiac work, is the first clue to a diagnosis of "primary" or "secondary" angina.

In secondary angina the assessment of the degree of impairment of coronary flow reserve, from carefully recorded history and by repeated electrocardiographic stress tests, provides the indication for coronary arteriography, performed with a view to coronary surgery. Only patients with severe secondary angina are potential candidates for coronary surgery for the treatment of their symptoms. Whether or not other patients are candidates for coronary surgery for improvement of prognosis is not one I can deal with now.

In primary angina, according to our experience, a vasospastic origin should be suspected in those patients with unstable angina at rest. However, patients with stable angina were also shown to have attacks of primary angina during ordinary daily activity,[79] and vasospasm has recently been demonstrated during stress testing[80 81] and cold exposure.[82] In fact, elevation of the ST segment, a reasonably reliable hallmark of acute vasospastic ischaemia, is sometimes observed during exertion.[28 83–86] Vasospasm can be demonstrated angiographically, by myocardial perfusion studies, and by reproducing electrocardiographic changes by provocative tests, which seem to have high specificity, but unknown sensitivity.[87–89] As a treatment of primary vasospastic angina, beta-blockers, the most widely used antianginal drugs, do not have the same rational indications as they do in secondary angina; they were found to be effective in some patients, but only at doses much higher than those sufficient to produce complete beta-blockade.[90] Nitrates and calcium antagonists[40 91] appear at present to be the most effective drugs in the treatment of vasospastic primary angina. Coronary bypass surgery does not appear to be a reasonable approach for relieving symptoms for patients with primary angina "unresponsive" to medical treatment, though in some patients operation might result in symptomatic relief as has been observed in the case of other now obsolete surgical procedures. Patients with mixed forms of angina may be candidates for bypass surgery, after medical control of their spontaneous attacks, if their exercise tolerance is much impaired. In a recent study,[92] coronary vasospasm has been shown to occur after bypass surgery, cardiac denervation, and autotransplantation. Prognosis depends on the one hand on the intensity and frequency of occurrence of vasoconstriction, and on the other hand on the underlying severity of coronary atherosclerosis, because any functional mechanism capable of reducing myocardial perfusion may be expected to have a more devastating effect in the presence of organic lesions.

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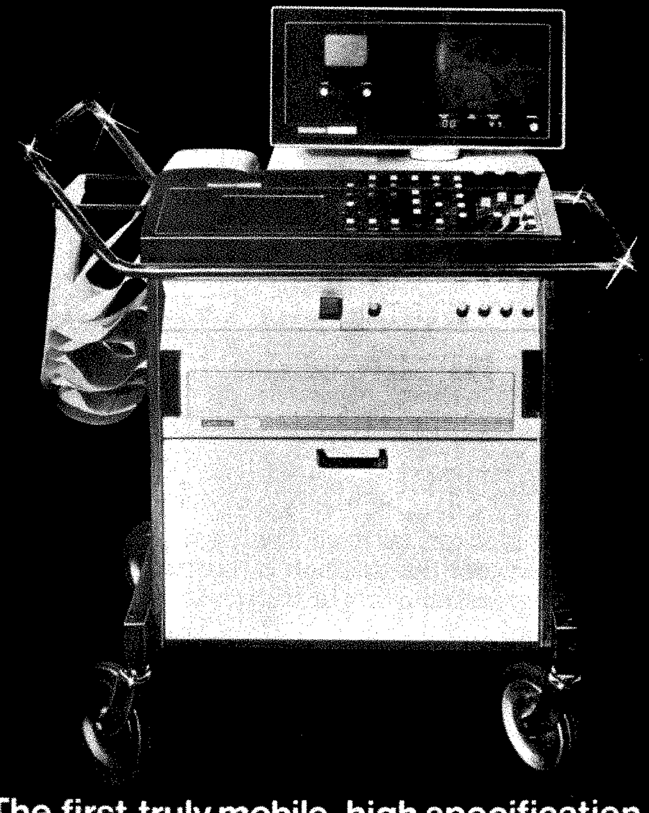

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Angina pectoris during inhalation of cold air

Reactions to exercise

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SUMMARY Twelve male patients, with effort angina and a history of cold intolerance, performed brief submaximal exercise bicycle tests with separation of inspiratory and room air. In one test, the patients exercised in a normal room (20°C), breathing either normal or very cold air (–35°C). In another test, environmental air was either normal or –10°C, and four combinations of inspiratory and room air were used: 20/20°C, –10/20°C, 20/–10°C, and –10/–10°C.

Inhalation of very cold air (–35°C) caused a significant decrease in maximal workload. Heart rate, systolic blood pressure, and rate-pressure product were significantly higher during exercise when compared with findings in the normal room. The decrease in maximal workload correlated significantly with the increase in heart rate and rate-pressure product during exercise. In five patients, the decrease in maximal workload exceeded 5 per cent. In contrast, inhalation of moderately cold air (–10°C) did not cause any significant changes in maximal workload or non-invasive variables. The decrease in maximal workload exceeded 5 per cent in one patient. Exposure to a cold room (–10°C), with inhalation of normal air, caused changes in maximal workload, heart rate, and blood pressure similar to those caused by inhalation of very cold air. Six patients showed a decrease in maximal workload exceeding 5 per cent.

In conclusion, skin cooling seems to be far more important in its effects on heart load and the working capacity in patients with effort angina than cold air inhalation in a moderately cold environment; inhalation of very cold air, however, does cause changes in working capacity and non-invasive variables similar to those of exposure to a cold environment. Increase in heart work during exercise is likely to cause the decrease in working capacity observed both with skin cooling and cold air inhalation.

Exposure to cold often causes a worsening of effort angina. In a previous investigation[1] we found that the decrease in work capacity in a cold environment was related to an increase in both heart rate and systolic blood pressure during exercise in the cold as compared with a normal environment. The relative importance of skin and airway cooling was not studied. The results of other investigations suggest that local cooling of the skin leads to an increase in heart work resulting from an increase in peripheral vascular resistance.[2] Reports on cold air inhalation have given conflicting evidence, both in studies at rest[3] and during atrial pacing.[4] To our knowledge there are no reports on the effects of breathing cold air at a normal room temperature on effort angina.

The aims of this investigation were to study the effects of cold air inhalation on patients with effort angina, at rest, during, and after exercise, and to correlate the changes in work capacity with changes in heart rate, blood pressure, and ST depression on the electrocardiogram. Studies were also carried out to determine whether the effects of cold air inhalation were different in normal and in cold environments.

Received for publication 3 April 1979

Subjects

Twelve male patients with a history of cold intolerance (all non-smokers, mean age 51 years, range 45 to 60) were invited to participate. All gave informed consent to the study, which had been approved by the Ethical Committee of the Medical Faculty. All patients had a history of stable angina pectoris for at least 12 months. Six patients had had one or more myocardial infarctions. All had exercise-induced angina and 0·2 to 0·6 mV depression of horizontal or downsloping ST segments on the electrocardiogram at the end of exercise. On a standardised stepwise ergometer test their work capacity, expressed as W_{max} 6 min[5] was on the average 100 W (range 70 to 150). In all patients this was limited by angina. None had hypertension, but one patient had symptoms and signs of chronic bronchitis. Six patients used beta-adrenergic receptor blocking agents in constant dosage, but no other treatment except short-acting glyceryl trinitrate was allowed.

Methods

ENVIRONMENT

Observations were made both in a cold environment in a special chamber and at normal room temperature. In order to separate the temperature of the environment from that of the inspired air, the patients breathed through a mouthpiece (dead space 15 ml) connected to an open pipe, 8 cm wide with suction at one end (Fig. 1) producing a slight negative pressure (0·1 kPa) at the mouth at end-expiration. Valves were not used, as they caused warming of the inspired air (5 to 15°C) (unpublished observations). Environmental temperatures were kept at 20 ±1°C (SD), with no wind and a relative humidity of 40 ±8 per cent, or at −10 ±0·4°C, with wind directed toward the face and trunk at a velocity of 2·2 ±0·1 m/s and an estimated relative humidity of 75 per cent. Temperatures of inspired air, measured 6 cm from the mouthpiece, were 20 ±0·2°C, −10 ±0·1°C, and −35 ±0·2°C. Temperature was measured with a copper/constantan thermocouple, wind velocity with a warm-wire anemometer, and relative humidity with a hair hygrometer.

In the room at normal temperature the patients were dressed in normal indoor clothing. In the cold chamber standardised clothing was added. The mean skin temperature was found to fall by 5·2°C during exercise in the cold environment (−10°C, 2·2 m/s). (For details, see Lassvik and Areskog.[1])

To obtain an estimate of the temperature changes in the airway, a very thin thermocouple (diameter 0·03 mm) was placed in the centre of the mouthpiece, 1 cm from the mouth. The mouthpiece was connected to a heated pneumotachograph and flow was integrated to volume. Temperature and volume of expiratory air were recorded on a high-frequency response X-Y recorder. The pneumotachograph was calibrated with known volumes. Two patients expired into the mouthpiece, immediately after inspiration of cold air (−10 ±0·1°C), at various respiratory rates, tidal volumes and forces of expiration. Thermocouples of this size have been shown to give true values of respiratory air temperature within wide ranges of air temperature and flow.[6]

TEST PROCEDURE

Two test situations were used. In the first, the patients exercised in a normal room, breathing either air at 20°C or very cold air at −35°C. Thus two conditions were obtained, temperatures of respiratory and room air being 20 and 20°C, respectively, or −35 and 20°C. The order of the tests was randomised and an initial trial test in the normal room was always performed, making a total of three exercise tests at each session.

In the second test, the patients exercised both in a normal room and in a cold room (−10°C), breathing either normal air or moderately cold air (−10°C). Thus four conditions were obtained, respiratory and room air temperatures being in turn 20 and 20°C, respectively, −10 and 20°C, 20 and −10°C, and −10 and −10°C (Fig. 1). The order of the tests was randomised and the tests were performed on a second day in reversed order. An initial trial exercise test was performed; thus, in all five serial exercise tests were performed at each session.

Exercise tests were performed in the sitting position on a bicycle ergometer (Siemens-Elema 380), with an initial load of 50 W increasing by 10 to 30 W per minute. Moderately severe angina was set as the endpoint of exercise, with a total exercise time of four to eight minutes. A six lead praecordial electrocardiogram (CH leads, with a forehead reference electrode) was recorded continuously at a paper speed of 10 mm/s. ST depression was measured at appearance of angina and at maximal workload from recordings at a paper speed of 50 mm/s. Heart rate was calculated from the recordings, and systolic blood pressure was measured by the cuff method. (For further details, see Lassvik and Areskog.[1])

The patients, sitting on the bicycle at ambient temperature, were connected to the mouthpiece, from five minutes before to four minutes after exercise. Heart rate and blood pressure were measured after five minutes sitting on the bicycle before exercise, every minute during exercise, just before stopping, and every minute for four minutes after exercise. The rate-pressure product (heart rate × systolic blood pressure) was calculated. Peak expiratory flow was measured with a Wright peak flow meter, 4·5 minutes after exercise. Rest intervals between tests were 30 minutes. During this time the patients were allowed to move around freely in a normal environment. During exercise the workload at appearance of pain and the maximal workload were noted. Measurements were also made during exercise at three minutes, when most of the patients had no pain, and at approximately 4·5 minutes, when all patients had angina. After exercise, the time for disappearance of pain was noted.

All tests were performed at the same time of day for each patient. Patients were not allowed to take food, nitrites, or muscular exercise for two hours before the tests. All patients had previously performed five serial exercise tests at normal temperature to establish reproducibility.[7]

STATISTICS

For each patient the mean values of the two sets of randomised exercises were calculated and evaluated using Student's t test for paired observations, and with regression analyses.[8]

Results

Inhalation of very cold air (–35°C) caused a significant decrease in the patients' work capacity, expressed as workload at appearance of pain and maximal workload, by 5 ± 1 per cent (mean ± SEM) ($p < 0{\cdot}01$) (Table 1). The decrease in maximal workload exceeded 5 per cent in five patients (Fig. 2). *Inhalation of moderately cold air (–10°C)* did not cause any decrease in either workload at appearance

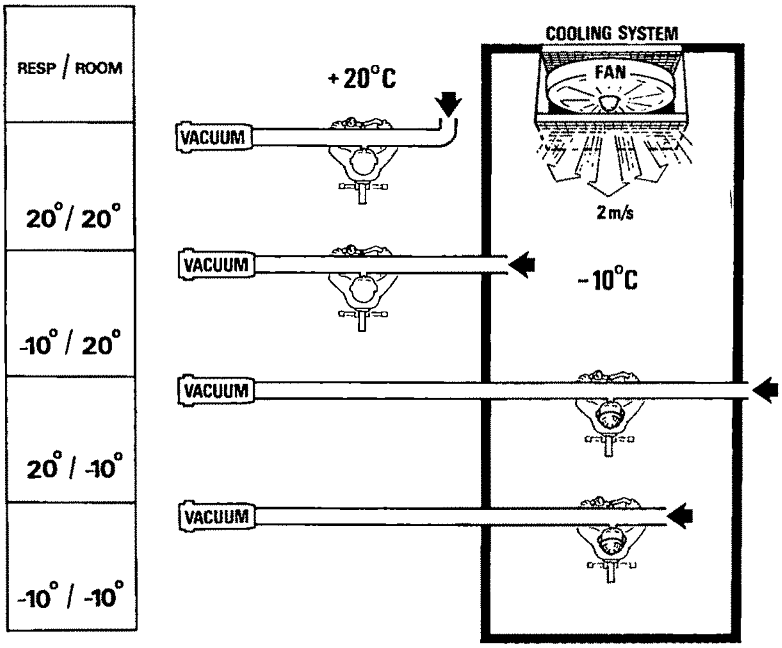

Fig. 1 *Separation of inhaled and environmental air. In another situation the patients breathed very cold air (–35°C).*

Table 1 *Work capacity, ST depression during exercise, and peak expiratory flow: values in normal room and changes in cold conditions*

	Temperatures (inhaled air/room)*				
	N/N (control)	*–35°C/N (absolute changes)*	*N/N (control)*	*–10°C/N (absolute changes)*	*N/–10°C*
Workload at appearance of pain (W)	122 ±9	–7 ±2†	119 ±9	–1 ±2	–8 ±2‡
Maximal workload (W)	146 ±10	–7 ±2†	142 ±11	–1 ±1	–7 ±2‡
Time for disappearance of pain (s)	126 ±26	46 ±34	118 ±21	3 ±35	–12 ±28
ST depression at appearance of pain (mV × 10)	1·6 ±0·3	0·1 ±0·1	1·5 ±0·3	0 ±0	0·4 ±0·2
ST depression at maximal workload (mV × 10)	2·5 ±0·3	0 ±0	2·6 ±0·3	0 ±0	0·1 ±0
Peak expiratory flow (l/min)	494 ±32	4 ±3	495 ±32	4 ±3	7 ±4

Mean values ± SEM.
* N = 20°C. † $p < 0{\cdot}01$. ‡ $p < 0{\cdot}001$.

of pain or maximal workload (1 ±0%) (Table 1) regardless of room temperature. The decrease in maximal workload exceeded 5 per cent in only one patient (Fig. 2). *Exposure to cold (–10°C) with inhalation of normal air* caused a significant decrease in workload at appearance of pain (7 ±1%) ($p<0.001$) (Table 1) and maximal workload (5 ±1%) ($p<0.001$) (Table 1), and the decrease of maximal workload exceeded 5 per cent in six patients (Fig. 2). In one patient very cold air inhalation caused a much greater decrease in maximal workload than exposure to the cold room (16% and 2%, respectively); otherwise differences between the two conditions were small.

Time for disappearance of pain, ST depression at appearance of pain and maximal workload, and peak expiratory flow values did not differ between any of the situations compared (Table 1). Several patients had occasional unifocal premature ventricular beats in the normal room, and the frequency of these did not increase on exposure to cold.

At rest, blood pressure and rate-pressure product were significantly higher ($p<0.01$) (Table 2) in the cold room than in the normal room. *During exercise,* heart rate, blood pressure and rate-pressure product were significantly higher both on inhalation of very cold air ($p<0.05$ for all variables) and in the cold room ($p<0.05$, $p<0.001$, and $p<0.01$, respectively). At maximal workload, blood pressure was significantly higher ($p<0.05$) in the cold room, whereas heart rate and rate-pressure product were unchanged compared with the normal room. *After exercise,* inhalation of very cold air was followed by significantly higher blood pressure at two and four minutes ($p<0.05$) and higher rate-pressure product at two minutes ($p<0.05$). Heart rate was significantly lower ($p<0.01$) in the cold room and blood pressure higher ($p<0.001$) two and four minutes after exercise, and rate-pressure product higher at four minutes ($p<0.01$). Inhalation of moderately cold air did not cause any changes in heart rate, blood pressure, or rate-pressure product at rest, during, or after exercise (Table 2).

During inhalation of very cold air, a significant correlation was found between the decrease in maximal workload and the increase in heart rate and rate-pressure product at three minutes' exercise ($p<0.05$ and $p<0.01$, respectively) (Fig. 3), and the increase of rate pressure product at 4·5 minutes ($p<0.05$). Likewise, in the cold room with inhalation of normal air, there was a significant correlation between decrease in maximal workload and increase in heart rate and rate-pressure product both at three and 4·5 minutes ($p<0.01$ and $p<0.001$, respectively).

Temperature of expired air after inhalation of

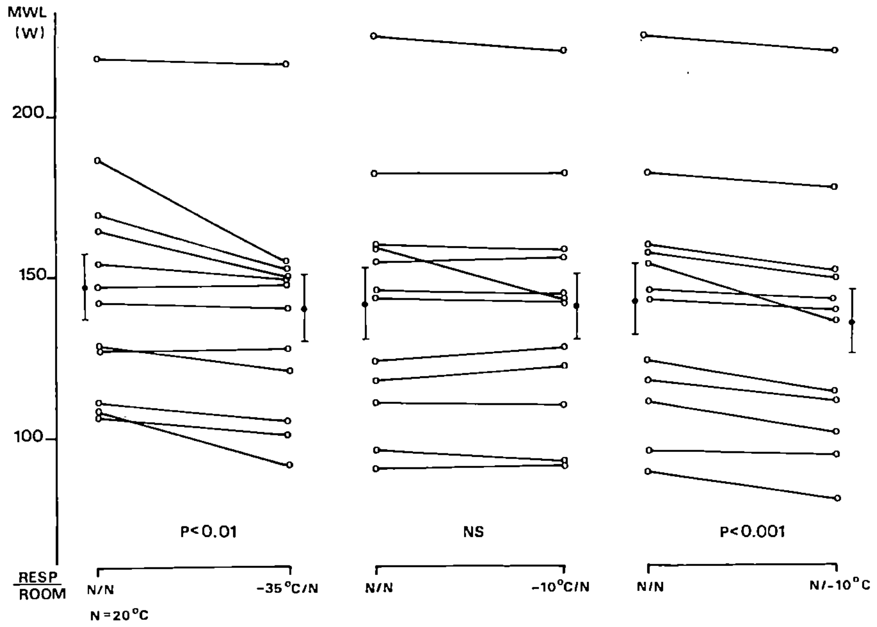

Fig. 2 *Changes in maximal workload (MWL) during inhalation of very cold air* (left), *during inhalation of cold air* (middle), *and on exposure to cold with inhalation of normal air* (right). *Bars show mean values ± SEM.*

cold air (–10°C): both on moderate and forced breathing (respiration rate 20/min and 42/min, respectively, and tidal volumes 1·2 and 1·7 litres, respectively) temperature increased from –5 ±0·1°C to 25°C within the first 100 ml of expiration and to 30°C within 200 ml (calculated as a mean of five consecutive breaths). During single breaths, with maximal force of expiration, temperature increased from –5·8 ±0·2°C to 25°C within the first 150 ml of expiration. The end-expiratory temperature was always 32 ±0·1°C. Measured dead space of the mouth was 70 ml.

Discussion

Inhalation of very cold air (–35°C) caused a significant decrease in work capacity in a group of patients with effort angina, all of whom gave a history of cold intolerance. In contrast, no changes in maximal workload were seen during inhalation of moderately cold air (–10°C), whether the environment was normal or cold. When the patients were exposed to a cold environment (–10°C) with inhalation of normal air, a significant decrease

Table 2 *Heart rate, systolic blood pressure, and rate-pressure product at rest, during, and after exercise*

	Temperatures (N=20°C) (inhaled air/room)*				
	N/N (control)	*–35°C/N (absolute changes)*	*N/N (control)*	*–10°C/N (absolute changes)*	*N/10°C*
Heart rate (beats/min)					
Rest	71 ±4	2 ±2	73 ±3	–2 ±1	1 ±2
Exercise 3 min	108 ±4	2 ±1*	110 ±6	1 ±1	3 ±1*
4·5 min	125 ±7	2 ±1*	127 ±7	0 ±1	3 ±1*
Maximal workload	131 ±7	–1 ±1	133 ±7	–1 ±1	–1 ±1
Recovery 2 min	80 ±6	–2 ±1	82 ±6	–1 ±2	–6 ±2†
4 min	76 ±5	–2 ±3	77 ±5	–1 ±1	–4 ±1†
Systolic blood pressure (mmHg)					
Rest	123 ±5	6 ±3	127 ±6	0 ±2	13 ±4†
Exercise 3 min	156 ±6	4 ±3*	155 ±8	0 ±1	9 ±2‡
4·5 min	163 ±6	3 ±3*	165 ±8	0 ±1	7 ±1‡
Maximal workload	167 ±7	3 ±3	171 ±8	–1 ±1	3 ±2*
Recovery 2 min	147 ±5	13 ±4*	154 ±6	4 ±3	21 ±4‡
4 min	129 ±4	10 ±3*	141 ±5	0 ±2	22 ±4‡
Rate pressure product (units $\times 10^{-2}$)					
Rest	88 ±7	7 ±2	94 ±8	–3 ±3	13 ±4‡
Exercise 3 min	169 ±14	7 ±3*	171 ±17	1 ±3	13 ±4†
4·5 min	203 ±14	5 ±3*	209 ±17	0 ±3	9 ±3†
Maximal workload	220 ±17	1 ±5	227 ±19	–2 ±2	2 ±2
Recovery 2 min	118 ±13	8 ±4*	176 ±13	1 ±4	7 ±5
4 min	99 ±9	5 ±4	109 ±10	–2 ±3	10 ±3†

Mean values ± SEM.
* $p < 0·05$. † $p < 0·01$. ‡ $p < 0·001$.

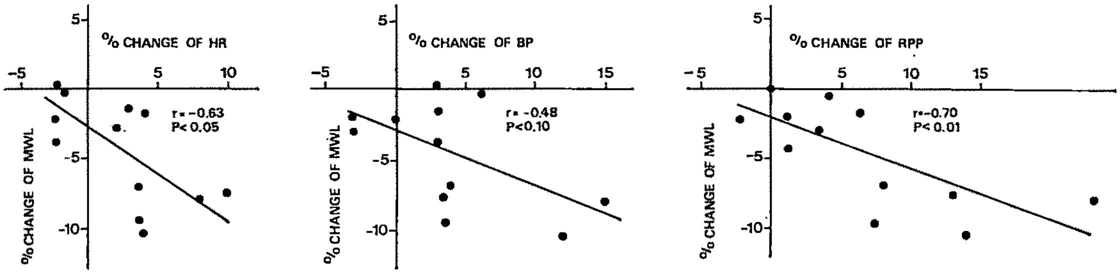

Fig. 3 *Correlation between changes of maximal workload (MWL), and changes in heart rate (HR), systolic blood pressure (BP), and rate-pressure product (RPP) during exercise (3 min) during inhalation of very cold air (–35°C).*

in maximal workload occurred, comparable to that found on inhalation of very cold air.

Thus it seems that though cooling of the airways may cause a decrease in work capacity in patients with angina, lower inhaled air temperatures are needed to reduce work capacity as much as with cooling the clothed body. One reason for this might be that heat losses via the airways are small compared with those via the skin, amounting to between 10 and 20 per cent of total heat loss.[9] The resulting fall in temperature in the lungs and the pulmonary venous blood is likely to be small, probably less than 0·2°C in the conditions used in this study (heat losses calculated according to Fanger[10]). Furthermore, our observations and those of others[9 11] indicate that cold air does not reach the alveoli in normal lungs, because inspired air is warmed in the upper airways. Since the venous blood from the upper airways returns to the right heart, cooled blood may never reach the left heart and the coronary arteries. The observations of Leon *et al.*[3] support this assumption, as only slight temperature changes were found in the left atrium, during inhalation of cold air (below –20°C) at rest.

During inhalation of very cold air, in this investigation, heart rate, systolic blood pressure, and rate-pressure product increased significantly during exercise, and a significant correlation was found between the decrease in maximal workload and the increase in heart rate and rate-pressure product. Since rate-pressure product at maximal load was not different in normal and cold situations, the increase of rate-pressure product at submaximal load probably reflects an increase in myocardial oxygen demand.[12] Thus, the decrease in work capacity during inhalation of very cold air is likely to have been caused by an increase in myocardial oxygen demand resulting from the increase in heart rate and blood pressure during exercise.

The cold-induced increases in heart rate, blood pressure, and rate-pressure product during exercise were similar on inhalation of very cold air and on exposure to a cold environment with inhalation of normal air, suggesting that the haemodynamic changes have the same cause. A further indication of this is that both with cold air inhalation and with exposure to cold, blood pressure was significantly higher after exercise than in normal conditions. Skin cooling is known to cause an increase in peripheral resistance and blood pressure as a result of stimulation of cold receptors and an increase in the sympathetic outflow to the skin vessels.[13 14] As cold receptors are situated not only in the skin but also in the mucous membranes of the airways, notably in the nose and tongue,[15] stimulation of cold receptors is likely to occur also with cold air inhalation. Since the cooled surface is smaller in the airways than in the skin, and cooling occurs mainly during inspiration, the total stimulation of cold receptors is probably less with cold air inhalation. This might explain why colder air is needed to produce the same changes in blood pressure during inhalation of cold air as with skin cooling.

Another interesting observation in this investigation was that cold caused greater increase in heart rate during exercise, in spite of a very short exposure to cold before exercise (five minutes). This indicates a reflex cause of the heart rate increase and confirms the observations of other investigators,[16] who found that exposure to an ice-cold shower was followed by an increase in heart rate and cardiac output within seconds. Thus, cold exposure probably causes an increase in the work of the heart not only because of an increase in afterload but also because of an increase in heart rate.

Other possible effects of exposure to cold are increase in left ventricular contractility,[3] increase in left ventricular end-diastolic pressure,[2] and increase in the cellular metabolism, caused by release of catecholamines.[17] Furthermore, Hattenhauer and Neill,[4] using atrial pacing, found signs and symptoms of myocardial ischaemia on cold air inhalation, at levels of heart rate and blood pressure well below those found during angina at normal temperature. As this could not be explained by left ventricular pressure changes, blood pH changes, or coronary angiographic changes, they suggested that spasm of minute coronary vessels caused the ischaemia. This possibility is also suggested by the findings of Mudge *et al.*[18] who noted decreased coronary blood flow during the cold pressor test, despite an increase in arterial blood pressure, in patients with coronary disease.

In conclusion, general skin cooling or inhalation of very cold air caused a decrease in the work capacity in about half of the patients investigated; this could be explained by a higher myocardial oxygen demand than during exercise at a normal temperature. With cold air inhalation compared with skin cooling, however, lower temperatures are needed to produce similar reduction in work capacity.

This study was supported by grants from the Swedish National Association against Heart and Chest Diseases and the County Council of Östergötland.

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Br Heart J 1980; **43:** 668–79

Haemodynamic and metabolic effects of atenolol in patients with angina pectoris

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SUMMARY Myocardial substrate extraction, coronary sinus flow, left ventricular pressure, and cardiac output were measured in 11 patients with angina pectoris at three pacing rates before and after atenolol (0·2 mg/kg). Left ventricular pressures, and the product of systolic pressure time index and heart rate did not change, but max dP/dt and KV max fell after atenolol. Only at the lowest pacing rate did the drug reduce cardiac output. Coronary sinus blood flow and myocardial oxygen uptake did not change after atenolol. At the highest pacing rate before atenolol four patients developed angina, accompanied by a rise in end-diastolic pressure. After atenolol angina was abolished in three, but the end-diastolic pressure still rose at the highest pacing rate. Myocardial lactate extraction ratio fell as heart rate increased, and was lower in the patients who developed angina. After atenolol, lactate extraction ratio increased significantly at the highest and lowest pacing rates. Myocardial pyruvate extraction rose after the drug. Arterial concentrations of hydroxybutyrate and acetoacetate fell after atenolol, but the decrease in their extraction was not significant. Myocardial extraction of free fatty acids was related to arterial concentration, which fell after atenolol. The changes in lactate and pyruvate extraction after atenolol were related inversely to changes in arterial free fatty acid concentration suggesting that the improvement in myocardial metabolism could have been secondary to reduced peripheral lipolysis. The increase in lactate extraction was associated with relief of angina, but did not abolish the rise in end-diastolic pressure induced by pacing.

The beneficial effect of beta-adrenergic blocking drugs in angina has been attributed to a reduction in myocardial oxygen demand secondary to their haemodynamic actions.[1–3] When heart rate is controlled by atrial pacing, beta blockade has little effect upon myocardial oxygen consumption.[4 5] Studies in which patients with angina have been paced before and after beta-blocking drugs have yielded conflicting results; some have shown no beneficial effect,[3 6] while others have shown an improvement in anginal threshold or lactate extraction,[4 7] suggesting that beta blockade may modify myocardial metabolism independently of its haemodynamic actions. The possible direct effects of beta-blocking drugs upon the human myocardium are poorly understood, and though their actions upon peripheral metabolism are well documented[8] the relevance of these to the heart has not been established.

Atenolol is a cardioselective beta-adrenergic antagonist without intrinsic sympathomimetic activity,[9] and is effective in the treatment of angina.[10] When heart rate is controlled, atenolol does not change myocardial oxygen consumption or coronary blood flow.[5] This study describes the effects of atenolol upon myocardial substrate extraction, coronary sinus blood flow, and systemic haemodynamics during pacing in 11 patients with angina, and attempts to identify the mechanisms by which it might improve the metabolism of the ischaemic myocardium.

Patients and methods

Eleven men (aged 40 to 59) were studied. All were limited by angina and were undergoing diagnostic cardiac catheterisation and coronary angiography. The patients gave written consent, and the hospital ethical committee approved the study.

Beta-blocking drugs were stopped 48 hours before catheterisation. All studies were performed in the morning after an overnight fast. Atropine 0·3 mg and diazepam 10 mg intramuscularly, and heparin 45 units/kg intravenously, were given one

Received for publication 12 November 1979

hour before catheterisation. Right and left heart catheterisations were performed via the right femoral vein and artery. Immediately after arterial catheterisation blood was taken for substrate concentration, and a second dose of heparin (45 units/kg) given. Coronary arteriography was performed using the Judkins technique, after which the patient was asked if he wished to continue with the metabolic study. A Ganz thermistor and pacing catheter (7Fr CCS 7U, Wilton Webster Inc) was introduced via a left antecubital vein and positioned in the coronary sinus. Its position was confirmed by injection of contrast medium. Cold saline was injected into the right atrium to ensure that the thermistors were unaffected by reflux of atrial blood.[11] A Schwarzer Swan-Ganz catheter was positioned in the pulmonary artery, and a catheter tip micromanometer, either no. 5 Millar or no. 8 Telco (MM52), introduced into the left ventricle. No measurements were made until at least 20 minutes after coronary arteriography. Coronary sinus pacing was established just above basal heart rate. Cardiac output, left ventricular pressure, and coronary sinus blood flow were measured, and left ventricular and coronary sinus blood were sampled simultaneously. The procedure was repeated at three pacing rates. Pacing was stopped and atenolol 0·2 mg/kg was given intravenously. Twenty minutes later, measurements were repeated at the same three pacing rates. Left ventricular cineangiography was performed after the metabolic study.

The pressure and coronary sinus thermistor signals were displayed on a Cambridge 12-channel recorder, and stored on tape. The micromanometer signal was differentiated either electrically or on-line by computer. KV max was derived from the plot of log d (developed pressure)/dt against pressure[12] by an electronic processor[13] or by computer. Systolic pressure time index was calculated from planimetric integration of the ventricular pressure trace. Cardiac output was measured by dye dilution. Indocyanine green was injected in the right atrium, and its concentration in the pulmonary artery sampled. The dye curve was analysed by an IVH3 Schwarzer cardiac output computer. Coronary sinus blood flow was measured by constant infusion thermodilution.[14] Left ventricular volume, ejection fraction, and mass were estimated from the right anterior oblique projection of the cineangiogram using a computer-light pen system.[13]

Blood was added to an aliquot of 10 per cent perchloric acid for deproteinisation and subsequent enzymatic photometric determination of lactate and pyruvate,[15] acetoacetate and hydroxybutyrate,[16] and glycerol.[17] For measurement of free fatty acids[18] blood was added to sequestrine tubes, mixed, and centrifuged. All samples were put on ice, and then stored at −20°C. Heparinised samples were taken for determination of oxygen content upon a Lex O_2 Con-TL (Lexington Instrument Corporation).

Extraction of a substrate is defined as the difference in concentration between arterial and coronary sinus blood (A–V). Extraction ratio is that difference expressed as a percentage of arterial concentration [(A–V)/A %]. Myocardial oxygen uptake is calculated as the difference between arterial and coronary sinus blood oxygen content multiplied by coronary sinus flow.

In addition to the 11 patients to whom atenolol was administered, one patient followed the same procedure, but was given saline instead of the drug.

The effect of heparin upon arterial free fatty acid concentration was investigated in a separate group of 21 patients who were undergoing diagnostic left heart catheterisation. In this laboratory all patients are given heparin (45 units/kg) after the introduction of the arterial catheter. Arterial free fatty acid concentration was measured immediately before, and five, 10, and 30 minutes after heparin administration. Of the 21 patients, 11 had received heparin at the time of premedication.

Statistical analysis is by Student's t test and linear regression; $p < 0·05$ is considered significant. Values are expressed as mean ± standard error of the mean.

Results

Ten of the 11 patients had abnormal coronary arteriograms, and the angiographic data are listed in the Table. One patient had angiographically normal coronary arteries, but a history of angina and a lactate extraction ratio of less than 10 per cent at the highest pacing rate.

As basal heart rate differed between individuals, the pacing rates used were not identical in all patients. In each individual the pacing rates before and after atenolol were in close agreement. The mean heart rates measured from the pressure records were 86 ± 2, 114 ± 3, and 140 ± 5 beats/min before, and 87 ± 2, 114 ± 3, and 139 ± 4 beats/min after atenolol.

The haemodynamic effects of atenolol are summarised in Fig. 1. Left ventricular systolic and end-diastolic pressures did not change significantly after atenolol. Cardiac output was reduced significantly only at the lowest pacing rate: 3·94 ± 0·22 l/min compared to 4·57 ± 0·32 l/min ($p < 0·05$). The maximum rate of pressure rise was lower after atenolol at each pacing rate, falling from 1667 ± 110 mmHg/s to 1501 ± 100 mmHg/s at the first placing rate ($p < 0{\cdot}01$), from 1878 ± 107 mmHg/s to 1551 ± 100 mmHg/s at the second ($p < 0{\cdot}01$), and from 2005 ± 151 to 1567 ± 146 mmHg/s ($p < 0{\cdot}01$) at the third pacing rate, and KV max fell from 75 ± 4 to 65 ± 3/s ($p < 0{\cdot}01$), 79 ± 4 to 64 ± 4/s ($p < 0{\cdot}01$), and from 63 ± 6 to 54 ± 4/s ($p < 0{\cdot}05$) at the same three pacing rates.

Four patients developed angina at the highest pacing rate before atenolol and, in these patients, between the lowest and highest pacing rates, end-diastolic pressure rose by a mean of 11 mmHg, whereas in the other seven patients there was a mean fall of 1 mmHg. After atenolol, three of the four did not have pain at the highest pacing rate, but end-diastolic pressure still rose by a mean of 11 mmHg, compared with a rise of 1 mmHg in the other seven.

Coronary sinus flow and myocardial oxygen consumption did not change after atenolol (Fig. 2). Arterial and coronary sinus blood oxygen content

Table *Details of coronary arteriography and left ventricular cineangiography*

Case no.	*Age (y)*	*RCA*	*LAD*	*Cx*	*Ejection fraction*	*LV mass (g)*
1	52	80%	50%	100%	0·43	217
2	56	100%	80%	80%	0·62	169
3	51	100%	100%	40%	0·56	215
4*	53	70%	90%	40%	0·72	178
5	40	Normal	100%	Normal	0·61	130
6*	48	100%	90%	80%	0·26	157
7	46	Normal	80%	Normal	0·84	246
8*	40	Normal	100%	70%	0·60	176
9*	43	100%	100%	70%	0·44	288
10	59	Normal	Normal	Normal	0·59	112
11	45	Normal	80%	Normal	0·60	132

RCA, right coronay artery; LAD, anterior descending branch of left coronary artery; Cx, circumflex branch of left coronary artery;
* patient developed angina at the highest pacing rate.
The percentage denotes the severity of the major lesion in that coronary artery, or its major branches.

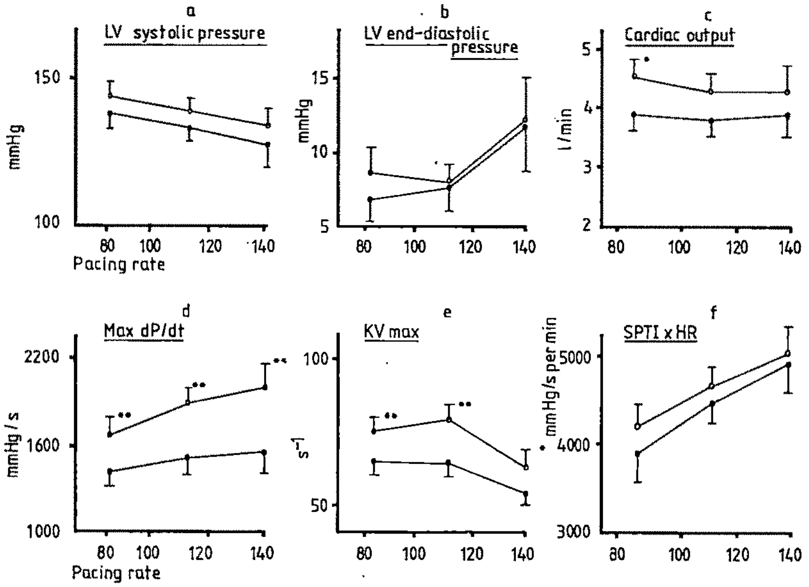

Fig. 1 *Haemodynamic observations at each pacing rate. Mean ± SEM of all 11 patients. Open circles: before atenolol. Closed circles: after atenolol. (a) Left ventricular systolic pressure. (b) Left ventricular end-diastolic pressure. (c) Cardiac output. (d) Maximum rate of rise of left ventricular pressure (max dP/dt). (e) KV max. (f) Product of systolic pressure time index and heart rate.* * $p < 0{\cdot}05$, ** $< 0{\cdot}01$, *when pre- and post-atenolol values are compared.*

did not change with increasing heart rate or after the drug, so coronary sinus flow closely followed myocardial oxygen uptake. Oxygen uptake/100 g myocardium was related to the product of systolic pressure time index and heart rate before atenolol, $r=0.68$ ($p<0.001$) and after atenolol, $r=0.62$ ($p<0.005$), and the slopes of the two regression lines were similar (Fig. 3). No differences in coronary sinus flow or myocardial oxygen consumption were apparent between the patients who developed angina, and those who did not.

Myocardial lactate extraction ratio fell as pacing rate increased; from 15·4 per cent ±2·7 at the first, to 0·8 per cent ±5·4 ($p<0.05$) at the third before atenolol, and from 26·6 per cent ±3·8 to 18·0 per cent ±4·2 ($p<0.05$) after atenolol (Fig. 4). The mean lactate extraction ratio of the 11 patients was higher after atenolol at each pacing rate, significantly so at the first, 26·6 per cent ±3·8 compared with 15·4 per cent ±2·7 ($p<0.02$), and at the third, 18·0 per cent ±4·2 compared with 0·8 per cent ±5·4 ($p<0.01$). There was a small increase in arterial lactate concentration from 0·575 ±0·035 mmol/l to 0·661 ±0·04 mmol/l ($p<0.01$) after atenolol. At the highest pacing rate before atenolol mean lactate extraction ratio in the four patients with angina was -12·6 per cent ±8·6, compared with 9·6 per cent ±4·2 in the patients without pain.

Arterial concentration and extraction of pyruvate, acetoacetate, hydroxybutyrate, and free fatty acids did not change as heart rate rose, so the results at each pacing rate are not considered separately. After atenolol arterial pyruvate concentration rose from 0·029 ±0·003 mmol/l to 0·039 ±0·002 mmol/l ($p<0.01$), and extraction rose from 0·005 ±0·001 mmol/l to 0·012 ±0·002 mmol/l ($p<0.01$). The increase in extraction ratio from 17 per cent ±7·5 to 31 per cent ±8 was not significant. Extraction was related to arterial concentration before, $r=0.58$

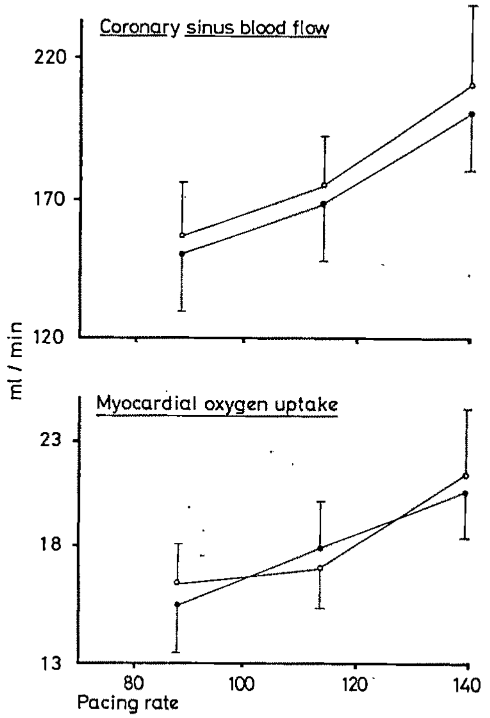

Fig. 2 Upper panel: *coronary sinus blood flow, mean ±SEM at each pacing rate.* Lower panel: *myocardial oxygen uptake, mean ± SEM at each pacing rate. Open circles: before atenolol. Closed circles: after atenolol.*

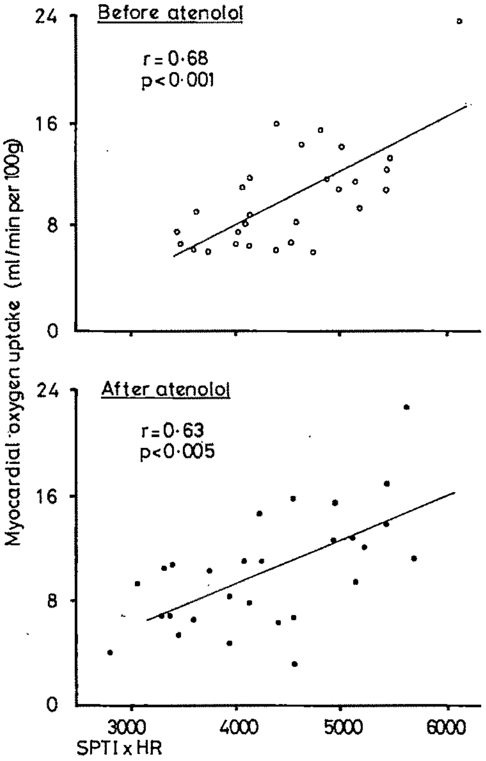

Fig. 3 *Relation between oxygen uptake/min per 100 g myocardium and the product of systolic pressure time index and heart rate (mmHg s/min).* Upper panel: *before atenolol. Oxygen uptake/min per 100 g = 0·0038 ± 0·0008 (SPTI × HR) – 6·78.* Lower panel: *after atenolol. Oxygen uptake/min per 100 g = 0·0032 ± 0·0008 (SPTI × HR) – 3·63*

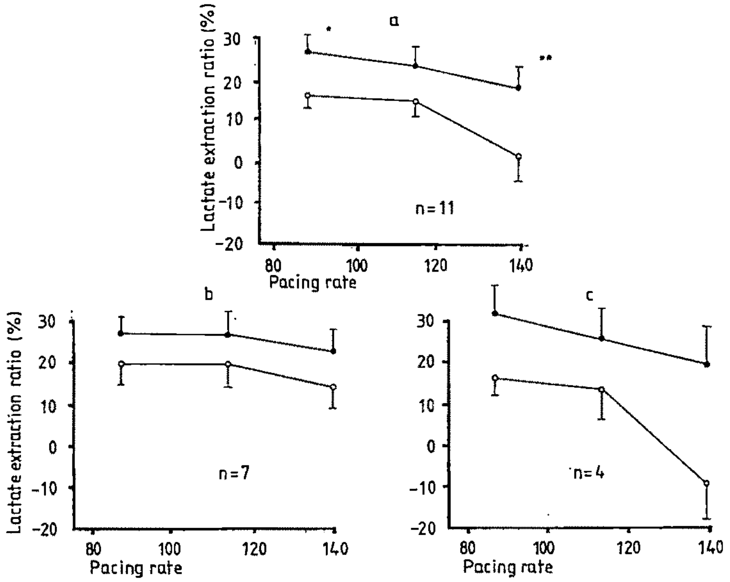

Fig. 4 *Myocardial lactate extraction ratio at each pacing rate. Open circles: before atenolol. Closed circles: after atenolol.* (a) *Mean* ± *SEM of all 11 patients.* (b) *Mean* ± *SEM of seven patients who did not develop angina.* (c) *Mean* ± *SEM of four patients who developed angina at the highest pacing rate before atenolol.* *$^*p < 0·02$, $^{**}p < 0·01$ when pre- and post-atenolol values are compared.*

(p < 0·01) and after atenolol, r=0·74 (p < 0·01) (Fig. 5). Arterial acetoacetate concentration fell from 0·087 ±0·012 mmol/l to 0·075 ±0·111 mmol/l, and extraction from 0·039 mmol/l to 0·033 mmol/l after atenolol, but these changes were not significant. Extraction ratios before and after atenolol were 45 per cent ±5 and 44 per cent ±6 (NS), and extraction was related to arterial concentration before and after the drug, r=0·80 (p < 0·001) and r=0·98 (p < 0·001).

After atenolol, arterial hydroxybutyrate concentration fell from 0·153 ±0·019 mmol/l to 0·111 ± 0·018 mmol/l (p < 0·01), but the fall in extraction from 0·044 ±0·006 mmol/l to 0·035 ±0·007 mmol/l was not significant. Extraction ratios were 29 per cent ±4 and 32 per cent ±4 before and after the drug. Extraction was closely related to arterial concentration; r=0·88 (p < 0·001) and r=0·96 (p < 0·001).

Arterial free fatty acid concentration fell after atenolol from 0·976 ±0·046 mmol/l to 0·743 ± 0·052 mmol/l (p < 0·001). Mean extraction fell from 0·172 ±0·02 mmol/l to 0·100 ±0·02 mmol/l (p < 0·01), but the decrease in extraction ratio from

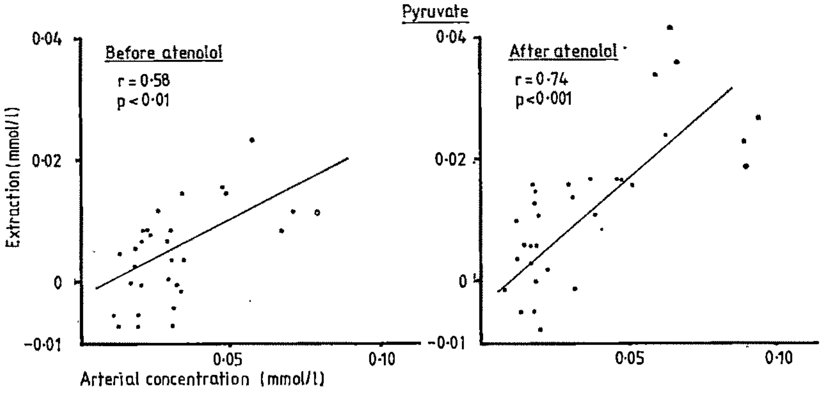

Fig. 5 *Relation between myocardial pyruvate extraction and arterial concentration of pyruvate.* Left-hand panel: *before atenolol. Extraction=0·255±0·066 (arterial concentration) – 0·002.* Right-hand panel: *after atenolol: extraction=0·415±0·035 (arterial concentration) – 0·004.*

17·6 per cent ±1·6 to 13·5 per cent ±2·6 was not significant. Extraction was related to arterial concentration before and after the drug; r=0·57 ($p < 0·001$), and r=0·44 ($p < 0·02$) (Fig. 6).

In Fig. 7 the change in myocardial lactate extraction observed in each patient at each pacing rate after atenolol has been plotted against the corresponding change in arterial free fatty acid concentration. The changes in lactate extraction were related inversely to the changes in arterial free fatty acid concentration; r= −0·603 ($p < 0·001$). A similar relation was found between changes in pyruvate extraction and changes in free fatty acid concentration; r= −0·607 ($p < 0·001$).

Arterial glycerol concentration decreased after atenolol from 0·060 ±0·003 mmol/l to 0·045 ±0·003 mmol/l ($p < 0·001$). Extraction was not related to arterial concentration, and glycerol release from the heart was common. At the lowest pacing rate after atenolol extraction was 0·008 ±0·003 mmol/l, compared with −0·007 ±0·002 mmol/l ($p < 0·01$) before the drug. At the higher pacing rates there was no significant change after the drug.

In 10 of the 11 patients arterial substrate concentrations were measured immediately before the second dose of heparin, approximately one hour before the metabolic study. Concentrations of hydroxybutyrate, acetoacetate, and free fatty acids

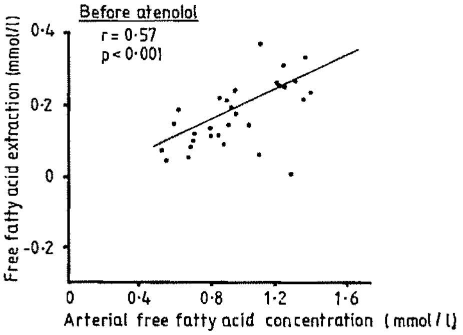

Fig. 6 *Relation between myocardial extraction and arterial concentration of free fatty acids.* Left-hand panel: *before atenolol. Extraction=0·225±0·069 (arterial concentration) – 0·025.* Right-hand panel: *after atenolol. Extraction =0·17±0·061 (arterial concentration) – 0·01.*

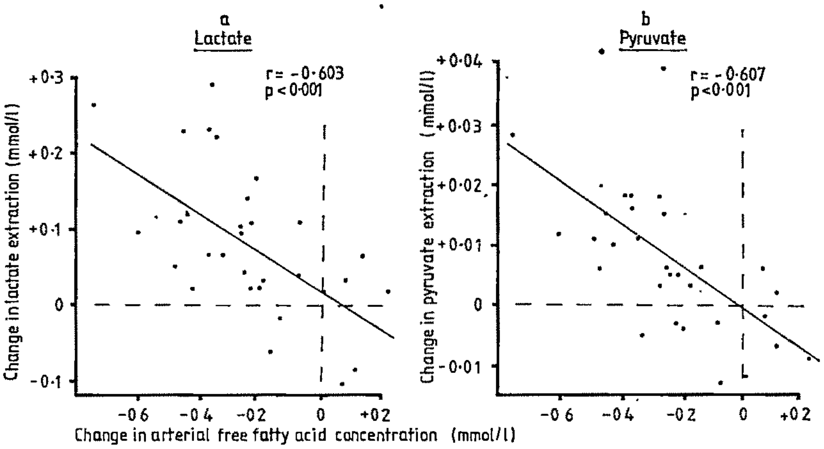

Fig. 7 Left-hand panel: *relation between the change in myocardial lactate extraction seen in each patient at each pacing rate after atenolol, and the change in arterial free fatty acid concentration. Change in lactate extraction = −0·252±0·043 (change in arterial free fatty acid concentration) +0·016.* Right-hand panel: *relation between the change in myocardial pyruvate extraction seen in each patient at each pacing rate after atenolol, and the change in arterial free fatty acid concentration. Change in pyruvate extraction = −0·034±0·007 (change in arterial free fatty acid concentration) −0.0005.*

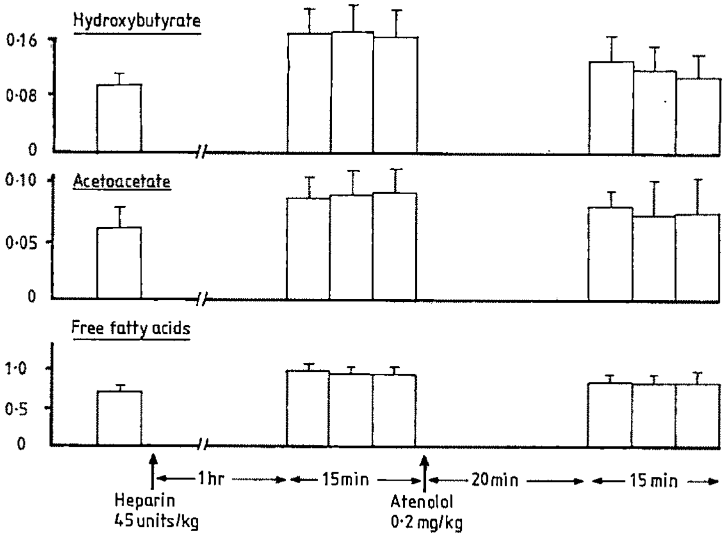

Fig. 8 *Arterial concentration (mean ± SEM) of hydroxybutyrate, acetoacetate, and free fatty acid before the second dose of heparin, at the three pacing rates before atenolol, and the three pacing rates after atenolol. The times at which these samples were taken in relation to heparin and atenolol administration are shown on the abscissa.*

were higher at the beginning of the metabolic study than before the second dose of heparin (Fig. 8). Their concentrations at the three pacing rates before atenolol showed little variation. Similarly, after atenolol concentrations were stable over the three pacing rates, though lower than pre-drug levels. Arterial concentration of lactate, pyruvate, and glycerol at the beginning of the metabolic study did not differ significantly from levels before the second dose of heparin.

The patient who followed the same procedure, but received saline instead of atenolol, proved to have only minor irregularities in the coronary arteries, and pacing did not precipitate pain. At the three pacing rates before saline myocardial lactate extraction ratios were 26, 30, and 32 per cent, and after saline, 24, 22, and 30 per cent. Arterial free fatty acid concentrations were 0·57, 0·63, and 0·56 mmol/l before, and 0·64, 0·53, and 0·56 mmol/l after saline.

Fig. 9 summarises the effects of heparin upon arterial free fatty acid concentration in the 21 patients undergoing routine catheterisation. The initial arterial free fatty acid concentrations were similar in both groups. In the 10 patients who had not been pretreated with heparin mean concentration rose from 0·69 ± 0·048 mmol/l to 1·244 ± 0·186 mmol/l ($p < 0{\cdot}01$) five minutes after heparin, and was still significantly raised at 10 minutes, 1·163 ± 0·16 mmol/l ($p < 0{\cdot}01$), though at 30 minutes, 0·982 ± 0·157 mmol/l, was not significantly different from the pre-heparin level. In contrast, in the patients who had received heparin at the time of premedication, arterial concentration did not rise significantly after the second dose of heparin, and mean concentration was similar before, 0·747 ± 0·067 mmol/l, and 30 minutes after heparin, 0·762 ± 0·122 mmol/l.

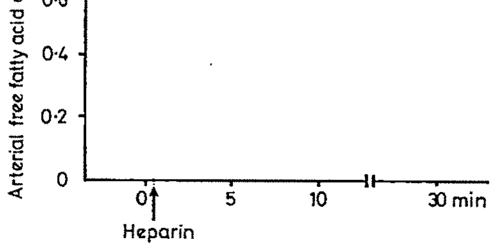

Fig. 9 *Effects of heparin on arterial free fatty acid concentration in 21 patients undergoing cardiac catheterisation. Open circles: mean ± SEM of 10 patients given a single dose. Closed circles: mean ± SEM of 11 patients who received heparin at the time of premedication in addition to the dose given after arterial catheterisation.* **$p < 0{\cdot}01$ *compared to pre-heparin levels.*

Discussion

In this study we used coronary sinus pacing to investigate the effects of atenolol upon myocardial metabolism and haemodynamics at progressively increasing levels of myocardial oxygen demand. We did not deliberately seek to induce angina, so the pacing rates employed were comparatively low. In a study using a similar procedure, pacing-induced changes in myocardial lactate extraction in both normal subjects and patients with coronary artery disease have been shown to return to normal within 15 minutes of stopping pacing.[4] To confirm this, one patient was given saline instead of atenolol, and it was found that both lactate extraction ratio and arterial free fatty acid concentration were comparable in the two periods of pacing.

All our patients were studied after coronary arteriography.

Injection of contrast media into the coronary circulation may increase myocardial blood flow (though oxygen consumption does not change[19]), depress myocardial contractility,[20] and produce a small rise in left ventricular end-diastolic pressure.[21] These effects are short lived and, as arteriography did not precipitate angina in any of our patients, it is likely that the interval of at least 20 minutes between arteriography and the first metabolic measurements was adequate to allow recovery.

Atrial pacing of the normal heart has little effect upon cardiac output, reduces stroke volume and end-diastolic pressure,[22 23] and increases max dP/dt and KV max.[24] In some patients with coronary artery disease pacing may fail to induce angina because the pacing rate required to produce pain is higher than the heart rate at which angina occurs during exercise; under these circumstances the haemodynamic response to pacing may be normal.[25] If angina does occur during pacing there is often an associated rise in left ventricular end-diastolic pressure[26 27] and a fall in V max,[28] though augmentation of max dP/dt by heart rate may be preserved. The rise in end-diastolic pressure has been attributed to acute failure,[27] or reduced diastolic compliance.[29] In our study the four patients who developed angina at the highest pacing rate before atenolol showed a rise in end-diastolic pressure, whereas in the other seven patients end-diastolic pressure fell as heart rate increased. The small number of patients does not allow a formal statistical comparison of the patients with and without angina, but it is of interest that after atenolol end-diastolic pressure still rose on pacing in the four patients who had experienced angina before the drug, despite relief of angina in three, and increased lactate extraction in all four. It might be argued that whereas the increase in end-diastolic pressure before atenolol was a result of reduced diastolic compliance secondary to ischaemia, the rise after the drug was the result of ventricular dilatation and failure caused by beta blockade. This explanation is unlikely because end-diastolic presure did not rise after atenolol in the other seven patients. These observations raise the possibility that when myocardial oxygen consumption is controlled by pacing, atenolol may have a more favourable effect upon lactate extraction than upon the mechanical properties of the ischaemic myocardium.

One mechanism by which beta-blocking drugs relieve angina is reduction of myocardial oxygen demand secondary to their haemodynamic actions.[2] The major determinants of myocardial oxygen demand are heart rate, contractility, and left ventricular wall tension.[30] As calculation of wall tension requires complex simultaneous measurement of ventricular volume and pressure, the product of systolic pressure time index and heart rate has been used to predict myocardial oxygen demand,[31] but suffers the disadvantage of being insensitive to changes in ventricular volume and contractility.[32] The haemodynamic effects of atenolol shown in this study are similar to those reported by Robinson *et al.*[33] Cardiac output fell at the lowest pacing rate; left ventricular systolic and end-diastolic pressures did not change. Max dP/dt and KV max were consistently lower at all pacing rates after the drug, suggesting that myocardial contractility was reduced, though conclusions drawn from indices derived from isovolumic pressure rise are open to criticism in the presence of ventricular asynergy.[34] Indices of contractility derived from quantitative angiography also fall after atenolol,[35] but end-diastolic volume rises, so that reduction in myocardial oxygen demand resulting from a decrease in contractility may be offset by an increase resulting from higher wall tension caused by ventricular dilatation. In agreement with other work[5] myocardial oxygen uptake did not change after atenolol when heart rate was controlled, and was still related to the product of systolic pressure time index and heart rate. Reduced contractility did not cause a fall in myocardial oxygen consumption, possibly because of the counterbalancing effect of increased wall tension caused by ventricular dilatation. The significant improvement in myocardial lactate extraction in our patients after atenolol occurred without reduction in oxygen uptake, or systolic pressure time index, and cannot be attributed to any haemodynamic change caused by the drug.

Coronary sinus blood flow did not change after atenolol and remained closely related to myocardial oxygen uptake. Redistribution of myocardial blood flow in favour of ischaemic areas has been suggested as a mechanism by which beta blockade relieves angina.[36] Atenolol does not increase venous drainage from the territory of a stenosed coronary artery,[5] nor does it increase perfusion in dyskinetic segments of left ventricular myocardium.[35] The metabolic effects of the drug are thus unlikely to have been the results of a direct action upon the diseased coronary circulation.

The energy requirements of the normal heart are met primarily by oxidation of free fatty acids, glucose, and lactate.[37] The citric acid cycle is the final common path for complete oxidation of all these substrates. Lactate by oxidation, and glucose by glycolysis, are both converted to pyruvate, which the heart can also extract from arterial blood. The entry of pyruvate into the citric acid cycle is controlled by pyruvate dehydrogenase, which is inhibited by high ratios of acetyl CoA : CoA and NADH : NAD.[38] High rates of fatty acid catabolism cause accumulation of acetyl CoA and NADH and inhibit pyruvate dehydrogenase, thus slowing the entry of pyruvate into the citric acid cycle. Ischaemia impairs the regeneration of CoA and NAD and may further inhibit pyruvate dehydrogenase. If pyruvate cannot be oxidised it is converted to lactate, and production of lactate and its release into coronary venous blood are characteristic findings in myocardial ischaemia.[39]

In normal subjects there is wide individual variation in myocardial lactate extraction.[40] As might be expected from the competition between pyruvate and free fatty acid metabolites for entry into the citric acid cycle, in a group of normal subjects myocardial lactate and pyruvate extraction are related inversely to arterial free fatty acid concentration ($r = -0{\cdot}62$),[40] and increase when free fatty acid concentration is reduced.[40] Thus, approximately 40 per cent of the variation in lactate extraction between normal individuals can be related to differences in arterial free fatty acid concentration, and lactate extraction in individual subjects can be changed by altering free fatty acid concentration. In a group of patients with coronary artery disease differences in severity of ischaemia lead to even wider individual variation of lactate extraction and/or production which may obscure the relation between lactate extraction and free fatty acid concentration. It is not surprising, therefore, that we found no relation between myocardial lactate extraction and free fatty acid concentration in our patients. But even in the presence of ischaemia, changes in arterial free fatty acid concentration might still affect lactate metabolism; lactate production by the ischaemic canine myocardium is increased when arterial free fatty acid concentration is raised,[41] suggesting an additive inhibitory effect of ischaemia and high rates of free fatty acid catabolism upon aerobic carbohydrate metabolism. In our patients the change in lactate extraction after atenolol bore a significant inverse relation to the change in arterial free fatty acid concentration. After atenolol mean free fatty acid concentration fell from 0·976 to 0·743 mmol/l, from which the published regression equation [lactate extraction $= 0{\cdot}37 - (\text{FFA})\ \text{ART} \times 0{\cdot}31$; $r = -0{\cdot}62$],[40] predicts an increase in lactate extraction of 0·073 mmol/l, compared with the observed mean increase of 0·081 mmol/l. Thus, the correlation coefficient and the slope of the regression line of the relation, which we found between change in lactate extraction and change in free fatty acid concentration, are similar to those described for the relation between lactate extraction and arterial free fatty acid concentration in normal subjects.

Studies upon human myocardial metabolism may be complicated by changes in arterial substrate concentration. Free fatty acid concentration may increase because of prolonged fasting, the stress of the procedure, or the use of heparin. We believe that adequate anticoagulation is mandatory for left heart catheterisation, and all the patients in this study were given heparin. Heparin raises free fatty acid concentration by activating lipoprotein lipase,[42] and its maximum effect is within about 10 minutes of administration.[43] The first dose of heparin, at the time of premedication, was given in an attempt to reduce circulating triglycerides, and thus reduce the effect of the second dose of heparin. The results of our study upon the 21 patients undergoing routine catheterisation show that heparin administration at the time of premedication is effective in blunting the rise in free fatty acid concentration that follows a second dose, and that in 30 minutes levels have returned to control values. The metabolic studies were made approximately one hour after the second dose of heparin, and it is unlikely, therefore, that arterial free fatty acid concentration measured then was influenced by the prior administration of heparin. That levels were higher at the beginning of the metabolic study than before the second dose of heparin may have been the result of stress. Arterial concentration was stable over the three pacing rates before atenolol administration; after the drug, arterial concentration was lower, but again similar at each pacing rate. In the patient who did not receive atenolol, free fatty acid concentration was comparable during both pacing runs. All these factors suggest strongly that the reduction in free fatty acid concentration observed after atenolol administration was the result of a direct action of the drug rather than a progressive decline in the action of heparin. These results are in agreement with the known peripheral antilipolytic action of atenolol.[44]

Although we were able to relate changes in lactate and pyruvate extraction to changes in arterial free fatty acid concentration, this statistical association may not be causal, even though a physiological basis exists for such a relation. Alternative mechanisms should be considered by which atenolol might increase myocardial lactate extraction without reducing myocardial oxygen consumption.

Experiments with labelled palmitate have demonstrated myocardial lipolysis,[45] which may provide an important source of free fatty acids for consumption by the myocardium.[46] Free fatty acids derived from this source might influence lactate and pyruvate metabolism by competition for entry into the citric acid cycle, or, particularly in the presence of ischaemia, by accumulation of long-chain fatty acyl CoA esters which inhibit oxidative metabolism.[47] Myocardial lipolysis is increased by catecholamines, and inhibited by propranolol.[48] In this study the moderate correlation between free fatty acid extraction and arterial concentration, the occasional negative extraction values, and the frequent finding of glycerol release all suggest that myocardial lipolysis was taking place. Atenolol increased glycerol extraction only at the lowest pacing rate, but did not appear to have any consistent effect at higher heart rates. Reduction in peripheral lipolysis was not, therefore, accompanied by an obvious reduction in myocardial lipolysis.

Adrenaline reduces the activity of pyruvate dehydrogenase, and this can be prevented by propranolol.[49] In the present study the fall in arterial free fatty acid concentration, and its likely effect upon lactate and pyruvate extraction, made it impossible to distinguish any similar direct action of atenolol upon pyruvate dehydrogenase. High ketone body consumption has been reported to reduce lactate extraction by the canine heart,[50] but in this study there was only a modest reduction in arterial concentration of hydroxybutyrate and acetoacetate after atenolol.

Coronary sinus blood contains venous effluent from both ischaemic and normal areas of myocardium. An increase in global lactate extraction could therefore be the result either of reduced lactate production by severely ischaemic areas, or of increased extraction by moderately ischaemic and normal areas, and these two mechanisms cannot be readily distinguished. The improvement in pain in three of the four patients with pacing-induced angina suggests that lactate production in ischaemic areas was reduced after atenolol, but the lack of effect upon end-diastolic pressure argues for the persistence of some ischaemia. The increase in lactate extraction after atenolol was greater in the patients in whom pacing had produced angina than in the other seven patients, but they also sustained a greater fall in arterial free fatty acid concentration after the drug. Thus, the effects of atenolol were qualitatively similar irrespective of the severity of ischaemia. The reason for the greater fall in free fatty acid concentration in these patients is not clear, but it is possible that they had greater sympathetic drive, or higher levels of circulating catecholamines, and therefore showed greater changes after beta blockade.

When heart rate is controlled by pacing the acute administration of atenolol increases myocardial lactate extraction without reduction of myocardial oxygen consumption or the product of systolic pressure time index and heart rate. This effect may be the result of a reduction of arterial free fatty acid concentration rather than of a direct action upon the myocardium. Inhibition of peripheral lipolysis may therefore contribute to the efficacy of atenolol in the relief of angina. These results emphasise the importance of measuring arterial free fatty acid concentration during studies upon myocardial lactate and pyruvate extraction, particularly in the investigation of antianginal drugs that may influence peripheral lipolysis.

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Br Heart J 1980; **43**: 680–8

Assessment of long-term plasma exchange for familial hypercholesterolaemia

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SUMMARY The effectiveness of repeated plasma exchange with 2 to 4 litres of plasma protein fraction as long-term treatment for familial hypercholesterolaemia has been evaluated in six severely affected patients receiving conventional cholesterol lowering treatment. Cell-separator mediated exchange at monthly intervals for one to two years reduced mean serum cholesterol levels from 18·5 mmol/l (715 mg/dl) to 12·4 mmol/l (480 mg/dl) in two female homozygotes but failed to influence xanthomata or prevent a two- to threefold increase in their left ventricular aortic systolic pressure gradients. More effective reduction of mean serum cholesterol levels from 15·7 mmol/l (608 mg/dl) to 8·6 mmol/l (333 mg/dl) in two male homozygotes by plasma exchange at fortnightly intervals for two to three years was accompanied by resolution of xanthomata and by stabilisation of aortocoronary lesions. In two male heterozygotes with angina, coronary angiographic appearances were unaltered or improved after one to two years of thrice-monthly plasma exchange, which reduced mean serum cholesterol levels from 6·4 mmol/l (248 mg/dl) to 4·7 mmol/l (182 mg/dl). We conclude that plasma exchange every one to two weeks, combined with oral nicotinic acid and/or cholestyramine, retards the rate of progression of atheroma in homozygotes and possibly induces regression in heterozygotes.

Familial hypercholesterolaemia is a dominantly inherited defect of beta- or low-density lipoprotein metabolism which affects approximately 1 in 500 persons in Britain[1] and North America.[2] The great majority of affected subjects are heterozygotes in whom the disorder is characterised by hyperbetalipoproteinaemia (type II hyperlipoproteinaemia) from birth, appearance of tendon xanthomata in early adult life, and the premature onset of coronary heart disease. Men have a 23 per cent risk of death from this cause before the age of 50.[3] The risk of premature death is even greater in the rare homozygotes who, as well as showing all the heterozygotes' features in an exaggerated form, in addition develop atheromatous involvement of the aortic root before puberty and show a pronounced resistance to cholesterol-lowering diets and drugs.

Four years ago we reported the feasibility of using plasma exchange to treat two patients with homozygous familial hypercholesterolaemia.[4] Since then we have treated a further four patients, two homozygotes and two heterozygotes, and have performed almost 300 plasma exchanges in the process. This paper provides evidence that the progressive accumulation of cholesterol in skin, tendons, and arterial wall which accompanies severe familial hypercholesterolaemia can be either arrested or partially reversed by combining conventional hypocholesterolaemic drug treatment with long-term plasma exchange. Some of the data have been published previously in abstract form.[5 6]

Subjects and methods

Clinical details of the six patients are shown in Table 1 and the duration and frequency of plasma exchange in Table 2. Both female homozygotes underwent this procedure at approximately monthly intervals, as previously described.[4] This was discontinued in case 1 after two years for social reasons; she subsequently underwent an aortocoronary bypass but died after operation. Plasma

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Received for publication 11 October 1979

Table 1 *Clinical details of patients with familial hypercholesterolaemia undergoing plasma exchange*

Genotype	*Case no.*	*Sex*	*Age*	*Serum lipids (mmol/l)**			*Drug treatment*
				TC	*TG*	*HDL chol*	
Homozygote	1	F	23	21·0	0·49	0·83	Resin + CPIB or NA
	2	F	26	16·1	2·21	0·67	Resin + CPIB, or NA or Neo
	3	M	25	15·5	0·90	0·72	Resin + NA
	4	M	15	15·8	1·10	0·65	Resin
Heterozygote	5	M	31	6·2	1·47	0·67	Resin + CPIB
	6	M	47	6·5	1·67	0·62	Resin

* While on low cholesterol diet and drug treatment, before starting plasma exchange.
TC, total cholesterol; TG, triglyceride; HDL chol, high-density lipoprotein cholesterol; Resin, cholestyramine 16 to 36 g/day; CPIB, clofibrate 2 g/day; NA, nicotinic acid 2 to 5 g/day; Neo, neomycin 2 g/day.
Conversion: SI to traditional units; Cholesterol 1 mmol/l≈38·7 mg/dl; triglyceride 1 mmol/l≈88·5 mg/dl.

exchange was discontinued in case 2 after 10 months because of increasing difficulty with venous access and she later underwent a portacaval shunt, as reported elsewhere.[7] She has since had an aortic valve replacement and triple aortocoronary bypass grafts. Both male homozygotes (cases 3 and 4) have been undergoing plasma exchange at one to two weekly intervals for two and three years, respectively, and are continuing to do so. Both are asymptomatic but each had sustained the loss of a homozygous teenage sib before starting plasma exchange. Both male heterozygotes presented with severe angina. One (case 5) underwent a successful aortocoronary bypass operation after 12 months of plasma exchange, whereas the second heterozygote (case 6) had sufficient relief from angina after nearly two years of plasma exchange to justify postponement of surgical intervention.

Plasma exchange was performed with an Aminco Celltrifuge on an outpatient basis, as described elsewhere.[4, 8, 9] Each patient's plasma was exchanged with 2 to 4 litres plasma protein fraction, anticoagulation being maintained with heparin. No significant complications have occurred except for some localised phlebosclerosis at venepuncture sites.

Clinical progress has been monitored by serial cineangiographic studies of the aorta and coronary arteries and measurement of left ventricular-aortic systolic gradients. By simultaneously projecting pre- and post-treatment films, paired frames were matched both anatomically and for phase of cardiac cycle and then made into composite slides. These were analysed "blind" by an independent observer, using a projection microscope to obtain ×10 magnified images on a ground-glass screen, which were then traced and measured.

Serum cholesterol and triglyceride concentrations were determined routinely[10] before each plasma exchange and, in some instances, immediately afterwards. Serum high-density lipoprotein cholesterol was determined as previously described.[4] The mean serum cholesterol level between exchanges was calculated by integrating the area beneath the rebound curve joining each post-exchange value to the subsequent pre-exchange value, and then dividing by the time interval between exchanges.

In four patients the faecal excretion of neutral sterols and bile acids[11, 12] was measured during the week before and the week after a single plasma exchange, at a time when they were in-patients in the Metabolic Unit, off all hypocholesterolaemic drugs and on a constant intake of dietary fat (P:S ratio 2:1), cholesterol (200 mg/day), and chromic oxide (1·5 g/day), which was given as a nonabsorbable marker.

Results

CHANGES IN SERUM CHOLESTEROL

During each procedure there was a rapid decrease

Table 2 *Overall serum cholesterol levels throughout period of plasma exchange*

Case no.	*Plasma exchange*				*Serum cholesterol (mmol/l)*		
	Started (date)	*Number*	*Duration (mth)*	*Volume (litres)*	*Minimum*	*Mean*	*Maximum*
1	9/74	24	22	2–2·4	6·1	13·4	16·1
2	1/75	9	10	2–2·4	5·5	11·4	13·2
	3/76	Portacaval shunt		—	—	13·2	—
3	10/75	66	38	3·2–4	4·4	8·7	10·8
4	8/76	78	28	2·4–3·2	4·0	8·4	10·7
5	6/76	33	12	3·2	2·4	4·9	6·0
6	4/77	72	23	3·2–4	2·0	4·4	6·1

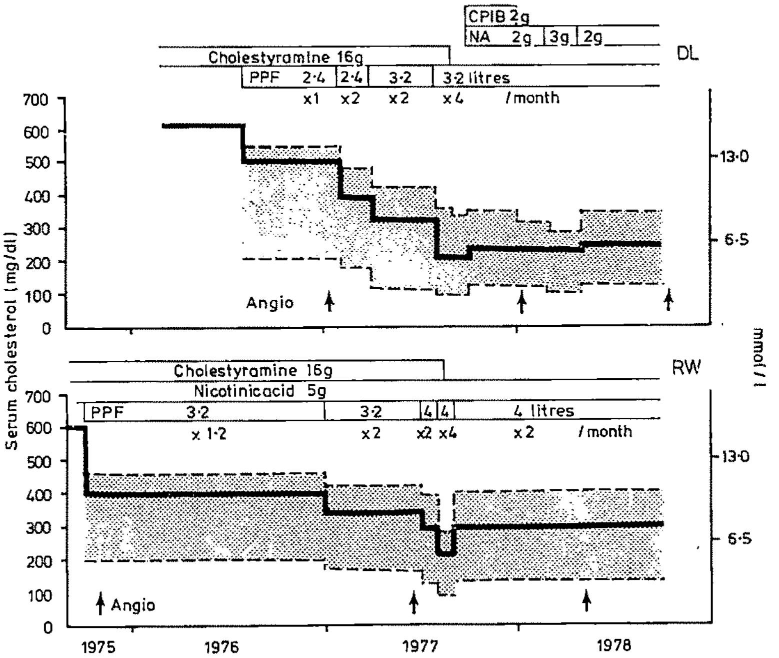

Fig. 1 *Serum cholesterol levels showing mean (solid line), maximum (upper border of stippled area), and minimum (lower border of stippled area) values observed in two homozygotes undergoing regular plasma exchange. The volume in litres of plasma protein fraction used and the number of exchanges per month are indicated above, together with the daily dosage of hypocholesterolaemic drugs administered. NA, nicotinic acid; CPIB, clofibrate. DL, case 4; RW, case 3.*

in serum cholesterol, followed by a slower rebound. The magnitude of the decrease depended upon the volume of plasma exchanged, averaging 70 per cent after a 4 litre exchange. The rate of rebound, which was damped by administering nicotinic acid 3 to 5 g/day to homozygotes and cholestyramine 16 g/day to heterozygotes, averaged 3·9 mmol/l (150 mg/dl) in homozygotes and 2·6 mmol/l (100 mg/dl) in heterozygotes during the first week after an exchange, and 2·0 mmol/l (77 mg/dl) and 0·9 mmol/l (35 mg/dl), respectively, during the second week.

Long-term fluctuations in serum cholesterol in patients undergoing plasma exchange at regular intervals can best be described in terms of the maximum or pre-exchange value, the minimum or post-exchange value, and the mean level between exchanges. These results are summarised in Table 2. The influence of the frequency and volume of plasma exchanged and of concomitant drug treatment is illustrated in Fig. 1 and 2.

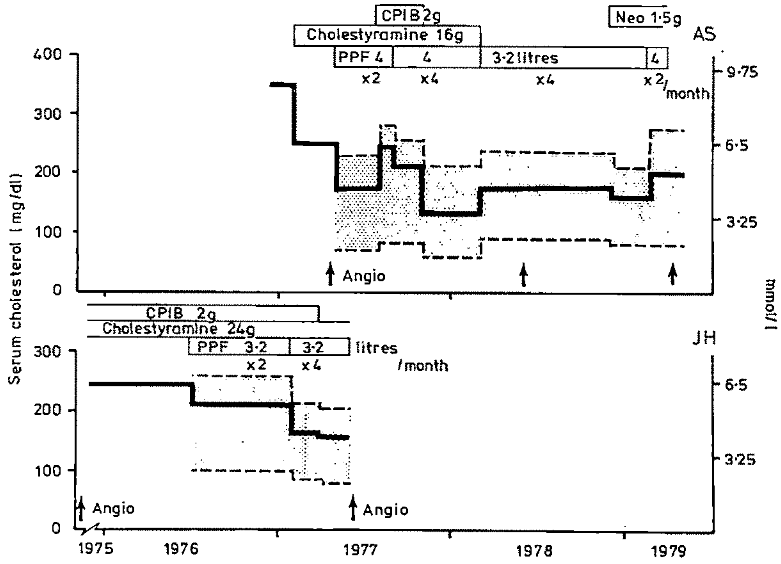

Fig. 2 *Serum cholesterol levels in two heterozygotes undergoing regular plasma exchange. AS, case 6; JH, case 5. Explanation of legend as for Fig. 1. Neo, neomycin.*

As shown in Fig. 1 the mean serum cholesterol in homozygote case 3 was reduced to less than 60 per cent of the level achieved by drug treatment alone when the latter was supplemented by 4·0 litre exchanges at fortnightly intervals. Similarly, 3·2 litre exchanges at weekly intervals reduced the mean serum cholesterol in homozygote case 4 by more than 50 per cent. Discontinuation of cholestyramine had no effect on serum cholesterol levels in either patient provided that nicotinic acid treatment was maintained.

Fig. 2 shows the results in the two heterozygotes. The mean serum cholesterol concentration in case 5 decreased from 6·2 mmol/l (240 mg/dl) on cholestyramine and clofibrate, to 4·1 mmol/l (160 mg/dl) during weekly 3·2 litre plasma exchanges. Case 6 presented with a serum cholesterol of 9 mmol/l (350 mg/dl), which decreased to 6·5 mmol/l (250 mg/dl) on cholestyramine and to 3·5 mmol/l (135 mg/dl) when administration of the latter was accompanied by weekly 4·0 litre plasma exchanges. Addition of clofibrate caused a sharp increase in serum cholesterol levels in case 6.

CHANGES IN XANTHOMATA AND FAECAL STEROID EXCRETION

Combined treatment with plasma exchange and nicotinic acid for two to three years has been accompanied by almost complete resolution of the cutaneous xanthomata of homozygotes cases 3 and 4, and by a pronounced reduction in the size of their tendon xanthomata, as illustrated in Fig. 3 and 4. No such changes were observed in cases 1 and 2.

Faecal excretion of neutral sterols and bile acids before and after a single plasma exchange in two homozygotes and two heterozygotes is shown in Table 3. Mean neutral sterol excretion increased from 613 to 767 mg/day during the week after plasma exchange, and bile acid excretion decreased from 498 to 420 mg/day. However, the only statistically significant difference was an increase in neutral sterol excretion in homozygote case 3 after a 4·6 litre exchange. Total faecal steroids averaged 1111 mg/day before and 1187 mg/day after plasma exchange.

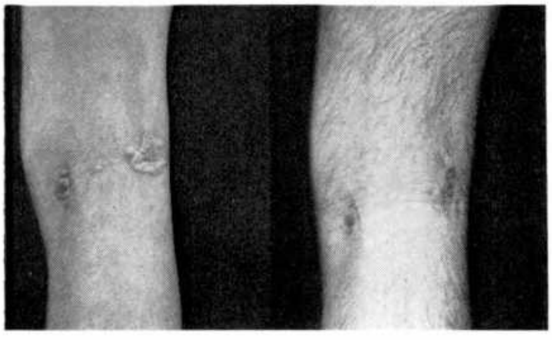

Fig. 3 *Cutaneous xanthomata in the right popliteal fossa of a homozygote (case 4) before and after two years of plasma exchange.*

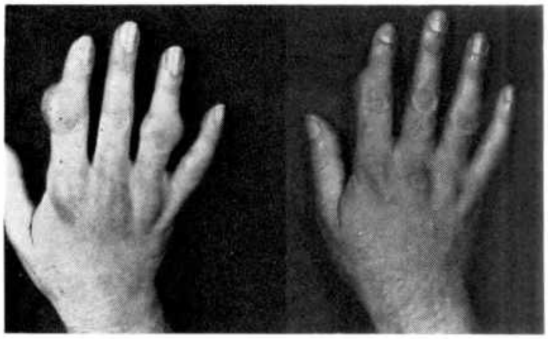

Fig. 4 *Tendon xanthomata over the interphalangeal and metacarpo-phalangeal joints of a homozygote (case 3) before and after three years of plasma exhange.*

ANGIOGRAPHIC APPEARANCES AND AORTIC GRADIENTS

At least two complete angiographic studies were performed in three of the homozygotes. As illustrated in Fig. 5 *(upper panel)*, the irregular and narrowed appearances of the supravalvular portion of the aorta and the right coronary ostium in case 3 have not changed during nearly three years of plasma exchange, nor was there any change in the aortograms of case 4 (Fig. 5, *middle panel*). However, the second study on case 2 showed left ventricular hypertrophy and a decrease in the mobility of her aortic valve cusps (Fig. 5, *lower panel*). Measurement of the ratio of the diameter of the narrowed aortic roots to that of adjacent unaffected segments, as shown in Table 4, confirmed the lack of change in

Table 3 *Faecal steroids in patients with familial hypercholesterolaemia during week before and week after plasma exchange with plasma protein fraction (PPF)*

Case no.	*Volume of PPF (litres)*	*Bile acids (mg/day)**		*Neutral sterols (mg/day)**	
		Before	*After*	*Before*	*After*
3	4·6	551 ± 58	531 ± 32	712 ± 40†	1051 ± 108†
4	2·0	577 ± 95	372 ± 8	266 ± 36	186 ± 13
5	4·0	281 ± 31	321 ± 51	621 ± 35	881 ± 81
6	4·0	583 ± 57	454 ± 89	851 ± 32	950 ± 166
Mean	3·65	498 ± 73	420 ± 46	631 ± 125	767 ± 197

* Values in each patient represent the mean ± SE of determinations on three to five samples collected during the week before and the week after plasma exchange, corrected for recovery of chromic oxide.

† $p < 0·01$ (Student's t test).

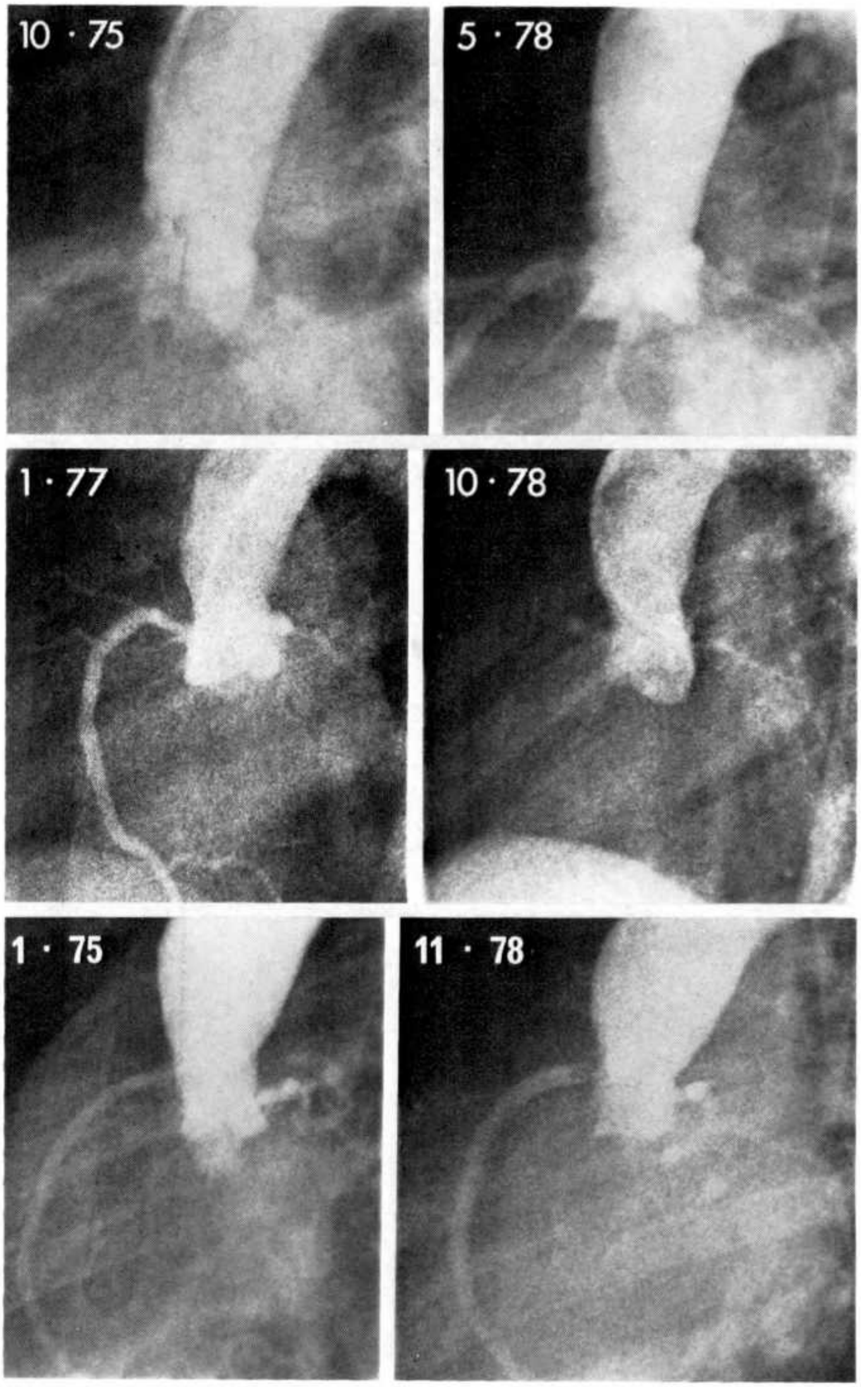

Fig. 5 Upper panel: *Aortograms in homozygote case 3 showing irregular contour and narrowing of the aortic root and right coronary ostial stricture before (10/75) and after (5/78) 31 months of plasma exchange.* Middle panel. *Aortograms in case 4 showing narrowed aortic root before (1/77) and after (10/78) 21 months of plasma exchange.* Lower panel: *Aortogram in case 2 showing narrowed aortic root before (1/75) and after (11/78) 10 months of plasma exchange followed by a portacaval shunt. Note the altered appearance of the aortic sinuses during the second study.*

any patient (excluding case 1, in whom an initial aortogram was not done).

The peak systolic gradient between the left ventricle and aorta was measured on at least two occasions in all four homozygotes, the results being shown in Table 4. Substantial increases occurred in cases 1 and 2 over periods of 26 and 46 months, in contrast to cases 3 and 4 in whom there was little change during 31 and 21 months, respectively. Mean serum cholesterol levels were considerably higher in cases 1 and 2 during the interval between angiograms (11·4 to 13·4 mmol/l or 440 to 520 mg/dl) than in cases 3 and 4 (8·4 to 8·7 mmol/l or 325 to 337 mg/dl), as shown in Table 2.

Each of the heterozygotes underwent two angiographic studies; both patients had normal aortograms but each showed bilateral atheromatous involvement of the coronary arteries. The appearances were unchanged in case 5 after nine months of cholestyramine alone followed by a year of plasma exchange (Fig. 6, *upper panel*). However, there was an apparent increase in the calibre of a stricture of the anterior descending branch of the left coronary artery in case 6 after a year of plasma exchange (Fig. 6, *middle panel*). There was no further change in this lesion after a second year but a decrease in the degree of dilatation of his ectatic right coronary artery proximal to the site of its occlusion was noted (Fig. 6, *lower panel*). Mean serum cholesterol levels were 4·4 to 4·9 mmol/l (170 to 190 mg/dl) in the two heterozygotes between plasma exchanges (Table 2).

Discussion

This paper analyses four years' experience with plasma exchange in the treatment of severe familial hypercholesterolaemia, the term severe encompassing both homozygotes and heterozygotes with coronary heart disease. The fact that six patients have successfully undergone a total of almost 300 plasma exchanges without serious complications attests both to the safety of the procedure and its acceptability to such individuals. In particular there was no instance of bacterial endocarditis in any of the homozygotes, whose diseased aortic valves renders them vulnerable to this risk. The reliability of the equipment used and the suitability of plasma protein fraction as an exchange fluid have greatly facilitated carrying out repeated plasma exchanges over prolonged periods. A commitment to treating homozygotes by this means should not prove too great a liability to any major centre equipped with a cell-separator because of the small number of patients likely to be involved. Plasma exchange is heavily dependent upon the availability of plasma protein fraction, however, and for this reason, we restrict its use in the far commoner heterozygotes to those with severe angina.

Table 4 *Left ventricular-aortic systolic gradients and aortographic appearances in homozygotes undergoing plasma exchange*

Case no.	*Date of angiogram*	*Gradient (mmHg)*	*Aortic ratio**
1	9/74	35	—
	11/76	75	—
2	1/75	34	0·59
	11/78	130	0·58
3	10/75	40	0·73
	5/78	50	0·71
4	1/77	19	0·67
	10/78	20	0·64

* $\dfrac{\text{Diameter of narrowed lumen}}{\text{Diameter of adjacent, normal lumen}}$

The use of plasma exchange to treat familial hypercholesterolaemia is based upon the premise that defective catabolism of low-density lipoprotein is largely responsible for the hypercholesterolaemia.[13,14] Physical removal of low-density lipoprotein from the intravascular compartment is therefore a logical approach, especially in homozygotes who respond poorly to drugs such as cholestyramine, which act by promoting low-density lipoprotein catabolism.[15] It is relevant that plasma exchange does not appear to stimulate low-density lipoprotein-apoB synthesis, especially since this is already somewhat higher than normal in homozygotes.[16] Furthermore, we found no evidence that plasma exchange caused any net increase or decrease in faecal steroid excretion, which is the normal pathway for removal of cholesterol; however, because these were non-steady-state studies it was not possible to deduce whether there was any change in cholesterol synthesis.

Streja *et al.*[17] recently described an association between coronary heart disease and reduced levels of high-density lipoprotein cholesterol in familial hypercholesterolaemia. Since plasma exchange decreases high-density lipoprotein levels still further it might seem to be deleterious. However, during the subsequent week the high-density lipoprotein (HDL) cholesterol concentration increases proportionally faster than the low-density lipoprotein (LDL) cholesterol and the HDL:LDL cholesterol ratio rises.[4,8] If one accepts that this ratio is an even more sensitive index of coronary heart disease risk than is high-density lipoprotein cholesterol,[17] then plasma exchange can be regarded as having a favourable effect, rather than the reverse.

Our data suggest that plasma exchange at monthly intervals does not control hypercholesterolaemia sufficiently well in homozygotes to prevent progres-

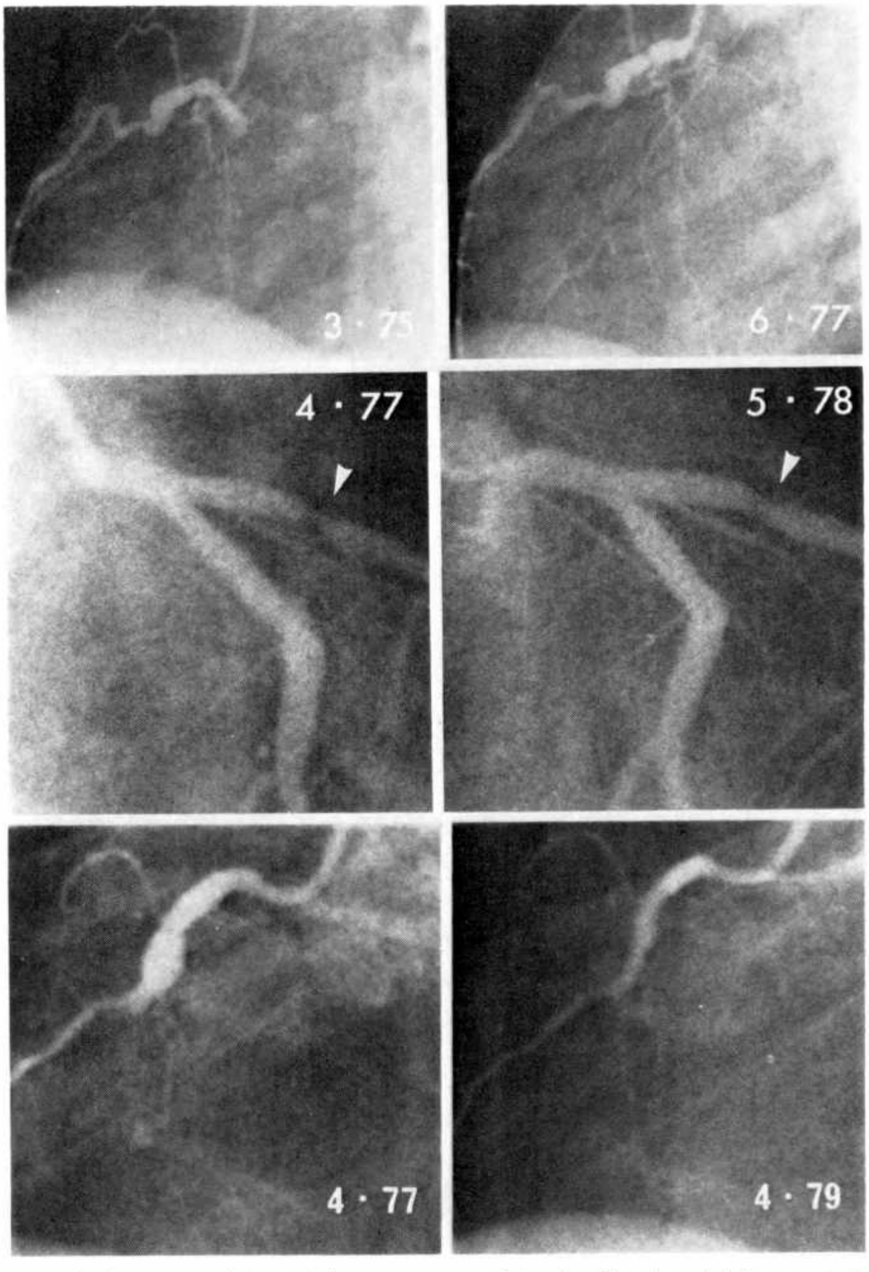

Fig. 6 Upper panel: *Coronary angiograms in heterozygote case 5 showing dilatation of right coronary artery proximal to site of occlusion before (3/75) and after (6/77) a period of conventional therapy followed by a year of plasma exchange.* Middle panel: *Coronary angiogram in heterozygote case 6 showing a stricture of the anterior descending branch of the left coronary artery* (arrowed), *before (4/77) and after (5/78) 13 months of plasma exchange.* Lower panel: *Coronary angiogram in heterozygote case 6 showing degree of dilatation of a partially occluded right coronary artery before (4/77) and after (4/79) two years of plasma exchange.*

sion of their disease. Both female patients developed a substantial increase in the systolic gradient between their left ventricle and aorta at a time when their serum cholesterol levels averaged about 13 mmol/l (500 mg/dl). It seems probable that a rising aortic gradient reflects progressive infiltration of the valve cusps, either by atheroma,[18] or fibrosis.[19 20] The threefold increase observed in case 2 occurred without any change in the degree of narrowing of the supravalvular part of her aorta and she was later found at operation to have a much fibrosed aortic valve. This was in spite of her having undergone a portacaval shunt three years previously which, unfortunately, resulted in only a transient fall in serum cholesterol.[7]

The findings in the two male homozygotes currently on plasma exchange are more encouraging. More effective reduction of hypercholesterolaemia by a combination of nicotinic acid and plasma exchange at one to two weekly intervals, using 3·2 to 4·0 litres of plasma protein fraction on each occasion, resulted in regression of both cutaneous and tendon xanthomata, indicating mobilisation of tissue cholesterol at these sites. Angiographic and haemodynamic studies suggest that their aortic lesions have not progressed over the past two to three years, during which their serum cholesterol levels averaged 8·6 mmol/l (333 mg/dl). Similarly encouraging results in a homozygote have been reported recently by Berger *et al.*,[20] who also found cholestyramine to be ineffective in slowing down the post-exchange rebound of serum cholesterol. The inability of cholestyramine to control hypercholesterolaemia in homozygotes is well documented[21 22] and contrasts with its effectiveness in heterozygotes.

Apparent angiographic improvement was observed in one of the heterozygotes (case 6), in whom there was an increase in the calibre of a stricture of the anterior descending branch of the left coronary artery after one year of weekly plasma exchange and cholestyramine, during which his serum cholesterol averaged 4·4 mmol/l (170 mg/dl), decreasing to 2·0 mmol/l (77 mg/dl) immediately after each procedure, and seldom rising above 6·5 mmol/l (250 mg/dl); the significance of the decrease in the degree of ectasia of his right coronary artery is difficult to evaluate in the absence of any information on blood flow. Spontaneous resolution of such strictures has been recorded, but not in patients with familial hypercholesterolaemia.[23] However, regression of early femoral atherosclerosis[24] and non-progression of advanced coronary lesions[25] have recently been claimed in heterozygotes whose hypercholesterolaemia was effectively controlled by conventional means. The even better control achieved by long-term plasma exchange provides a potential means of establishing whether rigorous reduction of serum cholesterol really can induce regression of coronary atherosclerosis in this situation. The advantage of small-scale, serial angiographic studies in answering this key question is that they assess the effects of treatment on atheromatous lesions more directly than do clinical trials, and are also shorter and less expensive; their main disadvantage is the difficulty of obtaining matching views and interpreting angiographic change.[26]

Although the arterial lesions of homozygous familial hypercholesterolaemia are indistinguishable histologically from atherosclerosis, except perhaps for the excessive number of foam cells present and the intensity of cholesterol deposition,[27 28] anatomically their distribution is distinctly unusual, with a unique predilection for the aortic valve, sinuses of Valsalva, and the aortic root. The supravalvular lesion also occurs in heterozygotes but without involvement of the aortic valve.[29] Coronary angiography reveals a high proportion of patients with ostial stenosis and triple vessel or left main stem disease.[30] Presumably these features reflect the hypercholesterolaemic basis of the underlying atheroma, as opposed to the multifactorial origins of coronary heart disease as found in the general population. Thus, any evidence of a beneficial effect of reducing serum cholesterol on the premature and severe lesions seen in familial hypercholesterolaemia should be interpreted with caution when considered in the wider context of atherosclerosis at large.

We thank the nurses who have helped run the cell-separator; Dr E Jepson for referring case 3; Saro Niththyananthan for determining faecal steroids; David Hawtin for making composite films of the angiograms and Hilary Stanbrook for analysing them. We also acknowledge the vital role played by Sir William Maycock and the Blood Products Laboratory, Elstree, Herts, in providing us with a constant supply of plasma protein fraction.

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Recording of left atrial potentials from pulmonary artery in man*

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SUMMARY The purpose of the present study was to validate the recording of left atrial activity from the pulmonary artery in man. Fifteen patients with atrial septal defect or patent foramen ovale were studied. Atrial activity was recorded simultaneously from the pulmonary artery and the high left atrium either during sinus rhythm or during paced ectopic atrial rhythm.

The results have shown a close similarity between the atrial signals recorded from the proximal (that is right-sided) high left atrium and the right pulmonary artery (overlying the vertebral column) both during sinus rhythm and paced ectopic atrial rhythm. Activity from the pulmonary arterial trunk corresponded best to signals from the lateral high left atrium. The latest activity, originating probably from the lateral left atrium, was recorded from the left pulmonary artery. However, in many cases the amplitude of the signals from the left pulmonary artery was too small to allow precise definition of the onset of atrial activity.

We conclude that recording atrial activity from the pulmonary artery is a valid approach for studying high left atrial activation if there is no direct access to the left atrium. When this technique is used in association with the recording of left atrial signals from the coronary sinus, left atrial activity can be analysed in detail.

Atrial mapping is of diagnostic significance for the analysis of the excitation sequence within the atria during atrial tachyarrhythmias and in re-entry tachycardias using retrogradely conducting accessory pathways.[1–3] For this purpose, techniques have been devised for recording right atrial potentials.[3–5] Direct access to the left atrium is usually difficult except for cases with a patent foramen ovale or with an atrial septal defect. Therefore, left atrial activity can usually be recorded only from the coronary sinus[6–8] or from the oesophagus.[9–11]

In the present study we wanted to see whether activity from the high left atrium could also be recorded from the pulmonary artery. A similar approach had previously been suggested by Kossmann *et al.*,[4] Puech,[7] Amat-y-Leon *et al.*,[12] and Ogawa *et al.*[13] However, these authors did not validate this approach by simultaneously recording atrial activity from the high left atrium and from the pulmonary artery.

Patients and methods

The recordings were done in 15 patients in the non-sedated postabsorptive state, in whom His bundle electrography was indicated for clinical reasons or in whom right heart catheterisation was performed for evaluation of an atrial septal defect. All patients had given informed written consent. Cardioactive drugs had been withdrawn before the study.

The recording techniques used in our laboratory have been described before.[14 15] For recording left atrial potentials a quadripolar electrode catheter was introduced into the high left atrium via a patent foramen ovale or an atrial septal defect. The interelectrode distance was 1·0 cm, with the distal electrode at the tip of the catheter. The distal electrode was positioned within the high left atrium at the margin of the lateral atrial wall. Electrograms from the pulmonary artery were recorded from a bipolar electrode catheter (4 F, electrode distance 0·5 cm; Cordis). Additionally, high right atrial potentials were recorded either by a bipolar electrode catheter or by changing the position of the quadripolar catheter from the high left atrium into the right atrial appendage. After recording

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* Partly supported by the Landesamt für Forschung, Nordrhein-Westfalen.

Received for publication 1 November 1979

atrial electrograms from the pulmonary artery, the bipolar catheter was withdrawn and used for recording low atrial potentials at the orifice of the inferior vena cava and of low septal activation from the His bundle recording site. All catheters were connected to an eight-channel direct writing recorder (Mingograph, Siemens-Elema) via a switchbox with isolated inputs.

In 10 patients (group 1), the following positions within the pulmonary artery were used for recording (Fig. 1): the pulmonary trunk (position 1), the right pulmonary artery overlying the vertebral column in the posteroanterior projection (position 2), an additional site within the right pulmonary artery at the lateral margin of the right atrium (peripheral right pulmonary artery, position 3), and from the left pulmonary artery (position 4). The onset of the P wave in lead II was used as a time reference.

In five patients (group 2), signals from the right pulmonary artery and the high left atrium were recorded simultaneously during both spontaneous sinus rhythm and paced rhythm from the low lateral right atrium.

In all cases at least five consecutive cycles were measured from which the mean values were derived. Statistical analysis was by Student's t test for paired data.

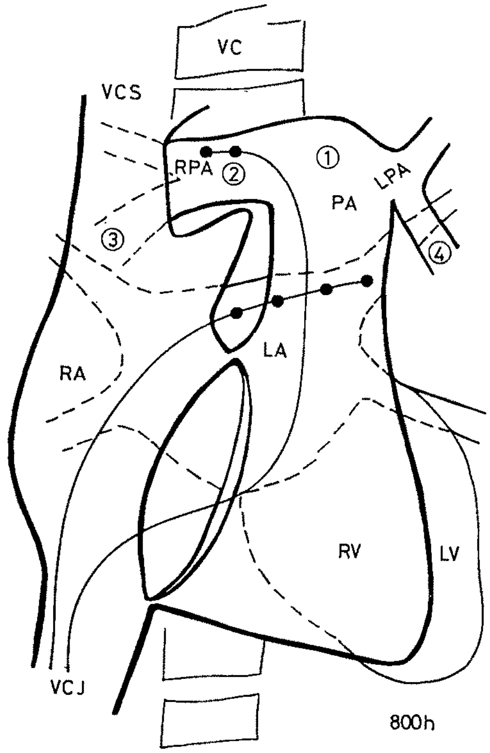

Fig. 1 *Schematic drawing of the heart showing the recording sites within the high left atrium and the pulmonary artery (PA). The electrodes of the catheters are indicated by large dots. For further details see method section.*

Results

Fifteen patients were studied (mean age 36·0 years, range 16 to 57 years). The clinical diagnoses and the intervals in the surface electrocardiogram are presented in Table 1.

In 10 cases (group 1, Table 2), an attempt was made to record atrial signals from the pulmonary trunk and—with one exception—from both right and left pulmonary arteries. The catheter could be manipulated into the right pulmonary artery in all cases. In three cases it was not possible to advance the catheter into the left pulmonary artery and in one case no attempt was made to reach it. In two cases the amplitudes were too low to record atrial activity from the left pulmonary artery. In two other cases the electrode catheter fell back into the right ventricle when withdrawing it from the right pulmonary artery; no further attempt was made to advance it again into the pulmonary trunk. In some cases, the atrial signals were too low for a clear distinction of the onset of atrial activity (Table 2).

Fig. 2 shows typical examples of recordings of

Table 1 *Clinical diagnoses, age, sex, and intervals in surface electrocardiogram in patients studied*

Case no.	*Age/Sex (y)*	*Diagnosis*	*P*	*PQ*	*QRS*
1	36/F	LBBB, patent foramen ovale	100	220	180
2	27/F	ASD (small)	110	180	80
3	40/M	ASD (large)	120	200	100
4	16/F	ASD (small)	80	170	85
5	17/F	ASD (small)	90	140	85
6	32/M	ASD (small)	100	170	120
7	22/F	Patent foramen ovale, VSD	90	150	75
8	40/M	CCM, VT, patent foramen ovale	100	230	90
9	46/F	ASD (large)	110	180	100
10	57/F	ASD (large)	110	150	120
11	38/F	Sinus bradycardia	90	160	90
12	29/F	Ventricular tachycardia	90	150	70
13	32/F	ASD (small)	100	180	70
14	53/M	Coronary artery disease, ventricular tachycardia	80	170	90
15	34/F	Atrial tachycardia	120	170	90
	34·6 ± 11·8 years		99·3 ± 12·8 ms	174·7 ± 25·6 ms	96·3 ± 27·6 ms

Abbreviations: ASD, atrial septal defect; VSD, ventricular septal defect; LBBB, left bundle-branch block; VT, ventricular tachycardia; CCM, congestive cardiomyopathy.

Table 2 *Sequence of atrial activation*

Case no.	*HRA*	HLA_{prox}	HLA_{distal}	$RPA_{per.}$	RPA_{vc}	PA_{trunk}	*LPA*	*A*	VC_{inf}
1	0	45	55	—	50	—	—	35	—
2	0	25	55	28	33	50	56	40	43
3	5	30	53	—	39	LA	—	50	—
4	20	38	55	30	35	LA	LA	30	—
5	0	54	56	28	24	LA	54	44	20
6	30	22	38	LA	49	55	68	50	57
7	25	27	46	—	14	42	—	40	40
8	0	30	55	—	25	—	—	45	—
9	5	49	66	10	29	LA	62	30	35
10	23	42	60	—	LA	54	LA	35	40
	10·8 ± 12·2	36·2 ± 11·0 (except for case 10: 35·6 ± 11·4)	53·9 ± 7·5	n=4 24·0 ± 9·4	n=9 33·1 ± 11·8	n=4 50·3 ± 5·9	n=4 60·0 ± 6·3	39·9 ± 7·4	n=6 39·2 ± 12·0

All intervals in ms; the onset of the P wave in lead II was used as time reference.
Abbreviations: HRA, high right atrium; HLA$_{prox}$, high left atrium proximal to the HRA; HLA$_{distal}$, high left atrium distal to the HRA; RPA$_{peripheral}$, right pulmonary artery, peripheral site (position 3 in Fig. 1); RPA$_{vc}$, right pulmonary artery in line with the vertebral column (vc) (position 2 in Fig. 1); PA$_{trunk}$, pulmonary artery trunk; LPA, left pulmonary artery; A, low septal atrial electrogram; VC$_{inf}$, low atrial electrogram at the orifice of the vena cava inferior; LA, low amplitude atrial signal not suitable for measuring onset of activation; —, this site was either not reached or no attempt was made to reach it.

atrial activity from various sites within the pulmonary artery, comparing it with the activity that was recorded directly in the high left atrium.

In Table 2, the results in the individual cases are presented. The high right atrium was activated at 10·8 ±12·2 ms (mean ± SD) after the onset of the P wave in lead II. Activity then spread to the right side of the high left atrium which was activated at 36·2 ±11·0 ms, and to the lateral high left atrium which was activated at 53·9 ±7·5 ms after the onset of the P wave in lead II. The signal from the right pulmonary artery overlying the vertebral column (position 2 in Fig. 1) coincided best with the activation time in the rightward part of the high left atrium, whereas the signal from the pulmonary trunk coincided with the lateral high left atrium. Mean activation time in the four cases in whom atrial activity could be recorded from both sites was 50·3 ±5·9 ms (pulmonary trunk) and 53·8 ± 11·6 ms (lateral high left atrium). The atrial signal recorded from the left pulmonary artery was recorded at 60·0 ±6·3 ms (n=4) after the onset of the P wave. For the four cases in whom atrial activity was also recorded from a more peripheral position in the right pulmonary artery, the atrial signal appeared at 24·0 ±9·4 ms.

The results in group 2 patients, in whom right pulmonary artery signals were compared with those from the high left atrium during sinus rhythm and a paced ectopic atrial rhythm, are presented in Table 3. An example of this type of recording is shown in Fig. 3. The difference between both signals ranged between −5 and 20 ms during sinus rhythm and between −2 and 25 ms during an ectopic atrial rhythm. The mean absolute differences between both signals during sinus rhythm and an ectopic atrial rhythm were not different.

Discussion

Sites used hitherto for endocardial atrial mapping in man were confined to the right atrium and the coronary sinus. Only occasionally could left atrial activity be recorded via a patent foramen ovale or an atrial septal defect. Several authors have reported their results on the recording of left atrial potentials from various sites outside the left atrium.[4 9 13 16] Kossman *et al.*[4] recorded potentials from the pulmonary trunk, which they attributed to the left atrium on the basis of the close anatomical relation between the pulmonary trunk and the high left atrium. Similarly, Puech,[7] and Latour and Puech[8] used the pulmonary artery for recording left atrial activity. Recently, this approach was again suggested by Amat-y-Leon *et al.*[12] in a case report. In this case, left atrial activity was recorded simultaneously with the atrial electrogram from the pulmonary trunk; activation occurred at the end of the P wave

80 ms after that in the high right atrium. Ogawa *et al.*[13] reported a close correlation between action potentials from Bachmann's bundle and the right pulmonary artery in experimental canine studies. In these studies, the atrial signals recorded in the right pulmonary artery coincided exactly with the activation of Bachmann's bundle in nine experiments and in seven other experiments the difference was less than 10 ms.[13]

The present study was directed towards validating this approach in man. Apart from a single case report,[13] previous studies have not recorded left atrial electrogram simultaneously[14] with that of the pulmonary artery. Therefore, we studied the relation between signals from the pulmonary arteries and the high left atrium.

The results have shown a close correlation between the atrial signals from the right pulmonary artery (overlying the vertebral column in the posteroanterior projection) and the high left atrial activity recorded from the rightward portion of the

Table 3 *Differences between activities from right pulmonary artery and high left atrium (that is RPA minus HLA) during sinus rhythm* (left panel), *and a paced rhythm from the lateral wall of the right atrium* (right panel)

Case no.	*Sinus rhythm (ms)*	*Ectopic atrial rhythm (ms)*
1	10	−2
2	20	10
3	−5	10
4	0	7
5	15	25
	8·0 ±10·4	10·0 ±9·7

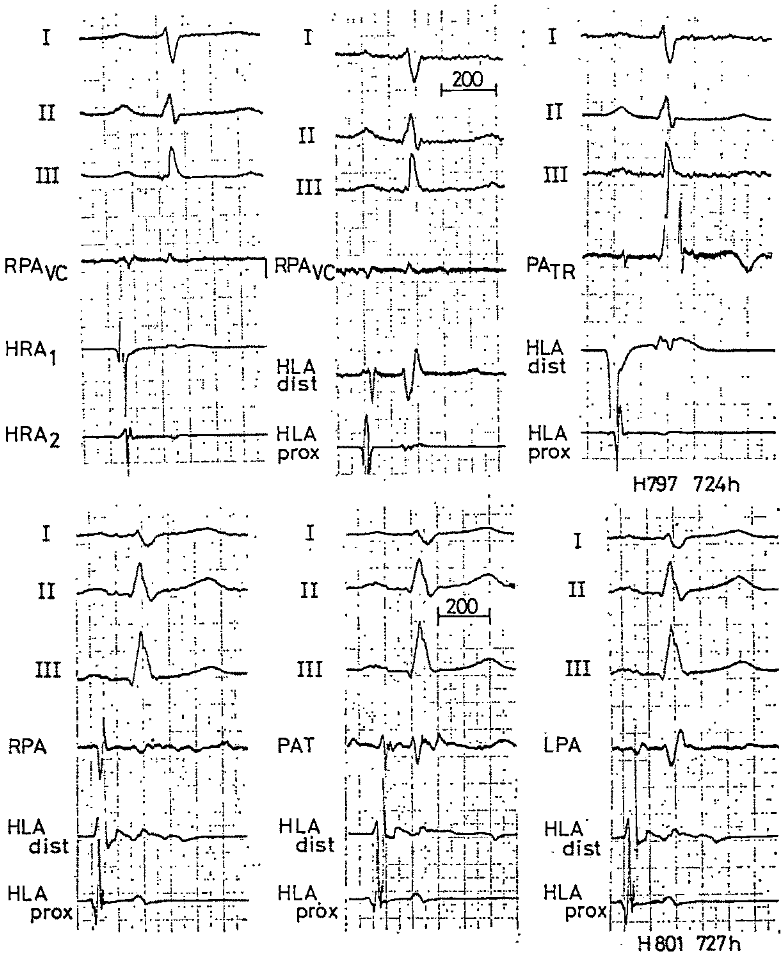

Fig. 2 Top: *Original recording in case 2 from the high right atrium (HRA), the high left atrium (HLA), and from three recording sites in the pulmonary artery. HRA_1 and HRA_2 were recorded from the proximal and distal pair of electrodes of a quadripolar electrode catheter introduced into the right atrial appendage. HLA_{prox} and HLA_{dist} are two recording sites within the high left atrium from the proximal and distal pair of electrodes of a quadripolar catheter (see Fig. 1). RPA_{VC} represents a signal from the right pulmonary artery overlying the vertebral column; PA_{TR} stands for pulmonary artery trunk.*
Bottom: *Case 6. The recording sites from the high left atrium (HLA) were similar to the one in the top panel. Recordings from the pulmonary artery were made from the right pulmonary artery (RPA), the pulmonary artery trunk (PAT), and the left pulmonary (LPA).*

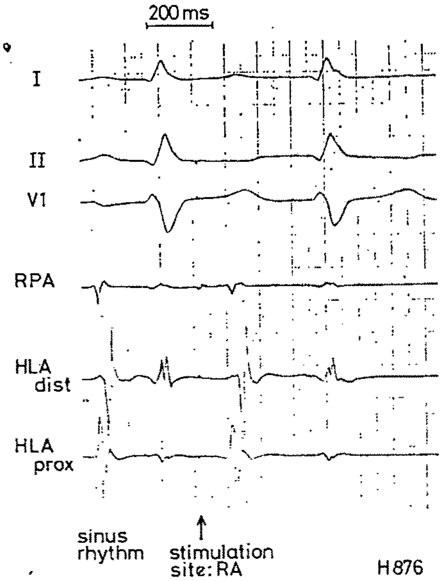

Fig. 3 *Original recording during sinus rhythm (first cycle) and after a premature atrial depolarisation that was introduced in the low lateral right atrium. Leads I, II, and V1 as well as three intracardiac leads are shown (for abbreviations, refer to Fig. 2). There is a close correlation in timing between the atrial activity recorded from the right pulmonary artery and the proximal (that is right-sided) left atrium during sinus rhythm and during ectopic atrial rhythm.*

high left atrium (Table 2). The mean difference between both sites was 3·1 ms, which is not significant. In the individual case, however, the difference between both sites of recording was more pronounced, ranging between 3 and 30 ms.

The simultaneous inscription of the electrograms from the pulmonary artery and the left atrium during sinus rhythm does not necessarily mean that the electrode in the right pulmonary artery is indeed recording high left artial activity. Both signals could well be generated via different pathways during sinus rhythm, occurring simultaneously only by chance. Therefore, both signals were also recorded during a paced ectopic atrial rhythm (Table 3, Fig. 3). They retained similar timing even when the origin of the rhythm was moved to the low lateral right atrium.

The amplitude of atrial signals recorded from the left pulmonary artery or the pulmonary trunk was sometimes inadequate for analysis (Table 2). In those patients in whom the signals were sufficiently large, the activity from the pulmonary trunk occurred 17·2 ms later on average than the activity in the right pulmonary artery (overlying the vertebral column). These signals correlated closely with the activation of the lateral parts of the high left atrium as recorded from the distal pair of electrodes of the quadripolar catheter. The signals from the left pulmonary artery were 9·7 ms later on average, than those from the pulmonary trunk. They represented the latest left atrial activation sites in our study.

Our results concerning the activation time within the right pulmonary artery are at variance with those reported by Puech.[7] He recorded the atrial activity at the origin of the right pulmonary artery, which is between our recording positions 1 and 2 (Fig. 1), 45 to 60 ms after the origin of the P wave, whereas in our study this signal occurred 33·1 to 50·3 ms afterwards. Furthermore, in his study the left pulmonary artery signals appeared after 75 to 90 ms (average 66 ms in our study). These differences might be the result of different sites of recording and of different degrees of atrial disease (as patients and not normal persons were studied). In our study in man, the differences in the activation times from the pulmonary artery and the high left atrium were much greater than in the experimental study by Ogawa *et al.*[13] This is probably because the exact site of recording could be less well defined than in an experimental model. Above all, our high left atrial signal does not represent exactly the activity from Bachmann's bundle as in the study by Ogawa *et al.*[13] but rather from ordinary atrial myocardium. Nevertheless, the right pulmonary artery seems to be a suitable site for recording proximal high left atrial activation if no other access to the left atrium is available.

Another possibility of recording left atrial activity is from the oesophagus.[8–11 17 18] Though it is a safe procedure, it is not as convenient for most patients as is the introduction of a catheter using the percutaneous approach. Furthermore, the isolated recording of left atrial potentials from the oesophagus without further recording sites and without the possibility of stimulating the atria does not yield sufficient information in most cases with complex arrhythmias. Additionally, introduction of an electrode catheter into the oesophagus may stimulate vagal reflexes which might influence the arrhythmia to be recorded and the electrophysiological indices of the atria and of the atrioventricular conduction system.

This study has validated the recording of left atrial signals from the pulmonary artery in man. It is therefore an extension of former studies which have suggested this approach.[4 12] The technique might be helpful for further delineating atrial activation sequence in cases with so-called sinus node re-entry. Using right atrial mapping, we were able to show that in these cases the atrial activation sequence during echo beats is similar to that of spontaneous sinus rhythm[3]; but we could not exclude the possibility that Bachmann's bundle rather than the high right atrium was the site of re-entry. The distinction is now possible by recording high left atrial potentials from the pulmonary artery. This may lead to a better understanding of the mechanisms of so-called sinus node re-entry. The method may also help to define the site of origin of ectopic atrial rhythms in man especially when used in association with recordings from the coronary sinus, for left atrial activation can be analysed in more detail both in anterograde and retrograde directions.

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Br Heart J 1980; **43**: 695–9

Chronic Q fever endocarditis

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SUMMARY Eight patients with chronic Q fever endocarditis were treated with tetracycline for up to 40 months. In addition, five of these patients received co-trimoxazole. Six patients had prosthetic valves. Two patients who had Q fever endocarditis on their native valves required valve replacement because of haemodynamic difficulties: in only one did the Q fever endocarditis contribute to the haemodynamic difficulty. One patient died.

It is suggested that medical treatment is continued until clinically and haematologically there is no evidence of endocarditis and the Q fever phase 1 antibody titre is less than 200. No recurrence of Q fever endocarditis has been detected in three of our patients who have now stopped treatment.

Q fever was first recognised as a clinical entity by Derrick[1] as a result of an outbreak of febrile disease among abattoir workers in Brisbane, Australia. It was shown by Burnet and Freeman[2] to be due to a rickettsia-like organism now classified as *Coxiella burnetii.*

Clinically acute Q fever may present as an atypical pneumonia or as a febrile illness which lasts two to three weeks. However, Q fever also exists in a chronic form, and endocarditis is a feature of the chronic disease.

This report describes the management of chronic Q fever endocarditis in eight patients. Six of the patients had prosthetic valves.

Patients and methods

From 1975 to 1979 we treated eight patients with chronic Q fever endocarditis from different areas of Northern Ireland. There were five men and three women, aged between 24 and 67 years (Table 1). Their occupations were farmer, farmer's wife, farm-feed salesman, housewife, labourer, two factory workers, and a civil servant. All the patients were either in contact with cattle or sheep or had drunk unpasteurised milk.

All patients had rheumatic valve disease. Six of the eight patients had previous heart surgery, where the valves had been replaced by prosthetic valves (Table 1). All valves removed at the time of operation were studied microscopically and showed no evidence of microbial infection.

Sera from the patients were tested against Q fever phase 1 and phase 2, psittacosis-lymphogranuloma venereum, and yolk sac antigens using the complement fixation technique as described by Bradstreet and Taylor[3] and the microtitre system. All antibody titres were expressed as reciprocals of

Received for publication 7 December 1979

Table 1 *Clinical data*

Case no.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Sex	M	F	M	M	F	M	M	F
Age (y)	33	40	67	37	34	52	24	57
Estimated duration of illness before diagnosis (wk)	4	12	4	6	6	12	4	12
Original valve lesion	M	M/A	M	A	M	A	M/A	M/A
Prosthetic valve/valves before Q fever	–	S–E	S–E	S–E	S–E	–	D–V C–E	S–E
Pyrexia	+	+	+	+	+	+	+	+
Hepatomegaly	+	+	+	+	–	+	+	+
Splenomegaly	+	+	+	+	+	–	+	+
Haematuria	+	+	+	+	+	+	+	+
Purpuric rash	–	+	+	–	–	–	–	–
Finger clubbing	–	+	–	+	+	–	–	–

M, mitral valve; A, aortic valve; S–E, Starr-Edwards valve; D–V, De Vega annuloplasty; C–E, Carpentier-Edwards valve.

Table 2 *Haematological data*

Case no.	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Hb (g)	9·5	12·0	7·8	8·7	13·3	14·0	14·5	10·3
ESR	42	72	60	150	61	14	5	125
Platelets	—	28 000	22 000	62 000	200 000	125 000	180 000	260 000
Gamma globulin	18·0	22·0	28·0	36·0	28·0	24·0	—	30·0
IgG	16·5	35·0	22·0	>30	18·5	24·0	—	29·0
IgA	—	—	4·50	—	—	7·0	—	4·50
IgM	3·5	2·4	1·8	>3	3·0	1·55	—	>3·5

Normal ranges: Platelets 150 to 450 000/µl; gamma globulin 7 to 15 g/l; IgG 5 to 16 g/l; IgA 1·25 to 4·25 g/l; IgM 0·47 to 1·7 g/l.

dilutions. Antigens and antisera were kindly supplied by the Standards Laboratory for Serological Reagents, Central Public Health Laboratory, London.

CLINICAL FEATURES OF PRESENTING ILLNESS

The estimated duration of the illness before diagnosis was from four to 12 weeks (Table 1). Six patients had prosthetic valves and, of the two patients without prosthetic valves, one (case 1) had severe mitral stenosis and the other (case 6) had aortic stenosis with regurgitation. On admission, all patients had pyrexia associated with night sweats. Seven patients had hepatomegaly, and seven patients had splenomegaly. The hepatic enlargement was from one to five finger breadths and the splenic enlargement was from one to eight finger breadths. All the patients had haematuria on ward testing. Two patients had purpura either at the time of admission or during the course of the illness.

HAEMATOLOGICAL FEATURES

Four patients presented with anaemia (Table 2). Six out of eight patients had a raised ESR (maximum 150 mm in the hour). Three patients had thrombocytopenia. The lowest platelet count recorded was 22 000/µl. Serum immunoglobulin studies were performed on seven of the eight patients. In all seven, gamma globulin and IgG were raised and in all but one of them IgM was also raised. All patients had more than three routine blood cultures which were negative.

DIAGNOSIS AND TREATMENT

The diagnosis was established by raised complement fixing antibody titres to phase 1 and phase 2 Q fever antigens (Table 3) along with clinical signs of endocarditis. No antibody was detected to psittacosis-lymphogranuloma venereum or yolk sac antigens. Seven of the eight patients had significantly raised phase 1 titres indicative of chronic infection. Though one of the patients (case 7) had a phase 1 antibody titre of 160 and a phase 2 antibody titre of 640 he had the clinical manifestations of endocarditis.

Six patients were treated medically and two had a combination of medical and surgical treatment (Table 3). All were started on tetracycline 2 g/day. Five patients were also given co-trimoxazole (trimethoprim 320 mg and sulphamethoxazole 1600 mg/day). During treatment the Q fever phase 1 and phase 2 antibody titres were monitored. Case 1 stopped co-trimoxazole after two-and-a-half months. Case 2 had co-trimoxazole for one week and then developed a rash which necessitated the drug's withdrawal. In one patient (case 5) tetracycline was discontinued after six months since no significant reduction in phase 1 and phase 2 antibody titres

Table 3 *Q fever phase 1 and phase 2 antibody titres*

Case no.	*Serum*	*Q fever antibody* *Phase 1*	*Phase 2*	*Months between first and last serum*	*Treatment period*	
1*	First	1280	5120	31	T —11 mth	T Co 29 mth
	Last	40	160		Co—2.5 mth	
2	First	1280	10 240	41	T —20 mth	
	Last	20	80		Co—1 wk	
3†	First	<10	<10	6	T —23 d	
	Last	5120	10 240			
4	First	10 240	10 240	17	T Co 24 mth	
	Last	1280	5120			
5	First	10 240	10 240	14	T — 6 mth	
	Last	1280	1280		Co—14 mth	
6*	First	2560	2560	31	T —21 mth	
	Last	40	160			
7	First	160	640	6	T Co 7 mth	
	Last	80	640			
8	First	2560	20 480	39	T —13 mth	
	Last	<10	40			

* Required surgery. † Died.
T, tetracycline (2 g/day); Co, Co-trimoxazole
(320 mg trimethoprim,
1600 mg sulphamethoxazole).

had occurred. Co-trimoxazole was then started and after two months of treatment a significant reduction in phase 1 antibody titre occurred. The remaining two patients (cases 4 and 7) have received tetracycline and co-trimoxazole for 24 and seven months, respectively, and continue with the treatment without side effects.

With the exception of case 3 who died after 23 days and case 7 who has been on treatment for seven months, the other six patients have shown a significant reduction in Q fever phase 1 and phase 2 antibody titres.

Of the surgically treated patients, case 1 had chronic Q fever endocarditis in association with severe mitral stenosis. After diagnosis he discharged himself from hospital. Two-and-a-half months later he stopped co-trimoxazole. He stopped tetracycline after 11 months. He was readmitted to hospital 15 months after the initial admission in distinct congestive heart failure. Despite bed rest, digoxin and diuretic treatment, and the restarting of tetracycline and co-trimoxazole, right ventricular failure persisted. At operation the severely stenosed and heavily calcified mitral valve was replaced by a Carpentier-Edwards valve. No vegetations were noted on the valve. His postoperative course was complicated by a left-sided hemiplegia which was not thought to be associated with Q fever endocarditis. Tetracycline and co-trimoxazole were stopped after continuing treatment for 29 months. During the period of treatment no prosthetic valve regurgitation was detected. Case 6, who was known to have mixed aortic valve disease, developed severe aortic regurgitation probably caused by Q fever endocarditis. Despite bed rest and treatment with tetracycline, digoxin, and diuretics, gross aortic regurgitation persisted. At operation the aortic valve was found to be thickened with retraction of all three cusps, calcified, and detached from one-third of the circumference of the aortic wall. No vegetations were noted. The aortic valve was replaced by a Hancock valve. The postoperative course was uneventful. He continued on tetracycline therapy for a total of 21 months. During the treatment and follow-up periods the Hancock valve has remained competent. The valves excised from these two patients were stained using Giemsa and Macchiavello stains. Both valves showed organisms consistent with *Coxiella burnetii*. Brown's modification of Gram stain, and PAS stain of both valves showed no bacteria or fungi.

The patient (case 3) who died was the oldest. He had a Starr-Edwards valve inserted in the mitral area for mitral regurgitation four years before the diagnosis of Q fever endocarditis. At the time of surgery he was noted to have poor left ventricular function. Postoperatively he continued in congestive heart failure. Seven months before death he was readmitted for further treatment of chronic heart failure. Q fever phase 1 and phase 2 antibody titres at that time were less than 10. However, three months before death he was again readmitted because of gross congestive heart failure. One month before death the Q fever phase 1 antibody titre was 5120 and the phase 2 antibody titre, 10 240. Treatment with tetracycline was begun. No surgery was contemplated in view of the poor left ventricular function. He died 23 days after starting treatment with tetracycline. No necropsy was carried out because of the danger to mortuary staff and pathologists.

Three patients (cases 2, 6, and 8) have now stopped treatment 20, 21, and 13 months, respectively, from starting it and have been followed-up from 18 to 41 months. At the time of stopping treatment all clinical signs of Q fever endocarditis had resolved. Haemoglobin and ESR were normal and phase 1 Q fever antibody titres were less than 200. One patient (case 8) who was treated with tetracycline alone, stopped treatment at 13 months. She had increased skin pigmentation which was proven on biopsy. However, clinically, haematologically, and serologically there was no evidence of Q fever endocarditis (phase 1 antibody titre <10). Subsequently the increased skin pigmentation resolved. During the period of follow-up there has been no evidence of recurrence of Q fever endocarditis. The longest period of survival since diagnosis has been four years.

Discussion

Although Q fever has a worldwide distribution, the first known case in Ireland was that of a Co. Down farmer with pneumonia in February 1962.[4] Before this, serological surveys carried out in the Republic of Ireland,[5] and in Northern Ireland[6] showed no evidence of Q fever infection. Subsequent studies[7–9] have confirmed that Q fever is now endemic in Ireland. In Northern Ireland from February 1962 until April 1979 138 cases of Q fever have been diagnosed. Also in Northern Ireland the first case of Q fever endocarditis was diagnosed in 1974 and 12 cases have now occurred. Three of these patients have died. Eight of these 12 patients came under our care.

The aortic and mitral valves are predominantly involved in Q fever endocarditis.[10] It has been suggested that thrombocytopenia is more common in Q fever endocarditis than in bacterial endocarditis. Turck *et al.*[10] found thrombocytopenia in 12 out of their 16 patients. Nevertheless, in our patients thrombocytopenia was found in only three patients. Gamma globulin fraction was raised in seven out of the eight patients and, as was noted by Turck *et al.*,[10] we found raised IgM and IgG fractions. The average duration of illness before diagnosis in our patients was much shorter than that recorded by other workers.[10] Only one of our patients developed an arterial embolus. None of our patients developed venous thrombosis, nor did they manifest significant hepatocellular damage during the course of their illness.

The diagnosis of chronic Q fever endocarditis is confirmed when antibody titres to both phase 1 and phase 2 antigens are raised. A phase 1 complement fixing antibody titre of greater than 200 is usually regarded as good evidence of chronic Q fever infection.[11] All our patients with the possible exception of case 7 had phase 1 antibody titres in excess of this. Antibody to phase 1 antigen does not normally develop during acute Q fever infection.

The management of chronic Q fever endocarditis is still controversial. In 1965, Ormsbee[12] stated that "Q fever endocarditis has been, so far as is known, uniformly fatal". Darrell[13] maintained that the antibiotics of choice, tetracycline and chloramphenicol on their own, never achieved a cure since they are rickettsiostatic rather than rickettsiocidal. Oakley[14] advocated valve replacement under antibiotic cover to eradicate infection. However, Wilson *et al.*[15] studied 16 patients with Q fever endocarditis and suggested that the infection can be controlled by prolonged tetracycline therapy. During treatment they showed a fall in phase 1 antibody titre. Turck *et al.*[10] using tetracycline and lincomycin in 14 patients with chronic Q fever endocarditis, also showed a reduction in phase 1 antibody titres. Freeman and Hodson[16] reported a fall in the phase 1 titres in a patient with Q fever endocarditis treated with tetracycline and co-trimoxazole for a period of slightly over four months. Operation was performed in the patients of Wilson *et al.*,[15] and Turck *et al.*[10] only for symptomatic and haemodynamic indications. We were able to treat five out of our six patients who developed Q fever endocarditis on prosthetic valves with either tetracycline or co-trimoxazole or a combination of these drugs for a prolonged period. No side effects were noted in patients on prolonged oral tetracycline treatment other than increased skin pigmentation in one patient. None of the patients has required an operation as their haemodynamic condition has remained satisfactory throughout the period of treatment and follow-up. Two patients whose native valves were damaged by rheumatic valvular disease required operation. However, in only one patient did the Q fever endocarditis contribute to the haemodynamic difficulty.

The response to treatment using tetracycline, either on its own or in combination with cotrimoxazole, was considered successful in six patients when improvement was noted clinically, haematologically, and by a fall in phase 1 and phase 2 antibody titres. One patient (case 7) has now been on treatment for seven months and has not shown a significant reduction in his Q fever phase 1 or phase 2 antibody titres, though clinically there has been no deterioration in his overall condition. Another patient with a prosthetic valve died from gross congestive heart failure caused by poor left ventricular function diagnosed before Q fever infection.

It has been suggested that after stopping treatment careful follow-up is mandatory to ensure that there is no recurrence of Q fever endocarditis.[10] Three patients have discontinued treatment after an average course of 18 months and have been followed up for on average 22 months. At the time of stopping treatment phase 1 and phase 2 antibody titres were less than 200. During the period of follow-up of the three patients there was no recurrence of Q fever endocarditis as judged clinically, haematologically, and serologically.

For the successful treatment of Q fever endocarditis tetracycline 2 g/day alone or in combination with co-trimoxazole (320 mg trimethoprim and sulphamethoxazole 1600 mg) per day should be given for a prolonged period. Co-trimoxazole therapy alone might be appropriate treatment but this is unproven. Surgery is indicated when significant haemodynamic difficulties occur but is rarely necessary to eradicate infection. *Coxiella burnetii* is very resistant to chemical and physical agents and the organism can remain viable for long periods in the environment.[17] Attempts to isolate *Coxiella burnetii* in the laboratory are hazardous to staff[18] and if an infected patient dies, pathologists and mortuary staff are at risk.[19] *Coxiella burnetii* has been isolated from the blood of a patient with chronic Q fever endocarditis during life and the vegetations from the aortic valve removed at necropsy showed high infectivity when inoculated intraperitoneally into guinea-pigs.[20] Presumably there is also a risk to operating theatre staff during open heart surgery, when infected valves are removed. Ideally, surgery should be carried out after a period of treatment with tetracycline and co-trimoxazole. This study indicates that if medical treatment is continued until all clinical signs of endocarditis have resolved, and haemoglobin and erythrocyte sedimentation rate have returned to normal, and Q fever phase 1 antibody titres are less than 200, then Q fever endocarditis does not recur.

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Br Heart J 1980; **43:** 700–1

Severe heart failure in child with ventricular septal defect and acute tricuspid regurgitation

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SUMMARY A case is reported in which acute tricuspid regurgitation developed in a child with a ventricular septal defect resulting in a left ventricular-right atrial shunt. This was successfully treated by closure of the defect and tricuspid valve replacement. The anterior leaflet of the tricuspid valve was almost completely destroyed by endocarditis, though in previous reports of tricuspid valve endocarditis in association with ventricular septal defect in children, it has been invariably the septal leaflet which is damaged.

Case report

A 2-year-old Libyan boy was referred for investigation because of shortness of breath and cyanosis. On examination he was small for his age and had mild central cyanosis and clubbing. He was in sinus rhythm with a raised jugular venous pulse and a marked V wave. The liver was enlarged 4 cm below the subcostal margin and was pulsatile. On auscultation there was a grade 4/6 systolic murmur accompanied by a thrill at the left sternal edge which increased in intensity on inspiration. There was a short grade 2/6 mid-diastolic murmur medial to the apex beat.

The chest radiograph showed moderate cardiac enlargement and pleonaemic lung fields. The electrocardiogram showed sinus rhythm, axis +120, right atrial hypertrophy, and right ventricular hypertrophy. Blood cultures were sterile. An echocardiogram showed abnormal tricuspid valve motion with a high amplitude vibration in the outflow tract of the right ventricle throughout the cardiac cycle (Fig. 1). The timing of tricuspid and mitral valve closure was normal. Cardiac catheterisation showed a bidirectional shunt at atrial level and a 5-mm gradient across the tricuspid valve. Angiography disclosed gross tricuspid regurgitation, the valve appearing completely flail. A ventricular septal defect was also seen. The tricuspid valve was attached normally at the atrioventricular ring. There was a large end-systolic volume in the right ventricle.

At operation there was obvious tricuspid regurgitation caused by almost total destruction of the anterior leaflet of the tricuspid valve. There were old vegetations on the small area of valve remaining, suggesting healed endocarditis (Fig. 2). There was a perimembranous ventricular septal defect and a persistent foramen ovale. The ventricular septal defect was closed by direct suture and a 27-mm Carpentier-Edwards porcine xenograft inserted in the tricuspid position. The persistent foramen ovale was closed by direct suture. The heart came off bypass without difficulty.

The patient made a satisfactory recovery and eight months later appeared to be extremely well, with no evidence of failure or of tricuspid regurgitation.

Discussion

Endocarditis of the tricuspid valve in association with a left-to-right shunt through a ventricular septal defect is uncommon, but has been described.[1] Inspection of the tricuspid valve in these cases reveals damage to the septal leaflet.[2] The unusual feature of this case was the damaged anterior leaflet resulting in its almost complete destruction. It has been shown experimentally by Wait and Mustard[3] that the septal leaflet of the tricuspid valve acts as a baffle against which the anterior and posterior leaflets synchronously close. Hence it is not surprising that in this case gross tricuspid regurgitation occurred.

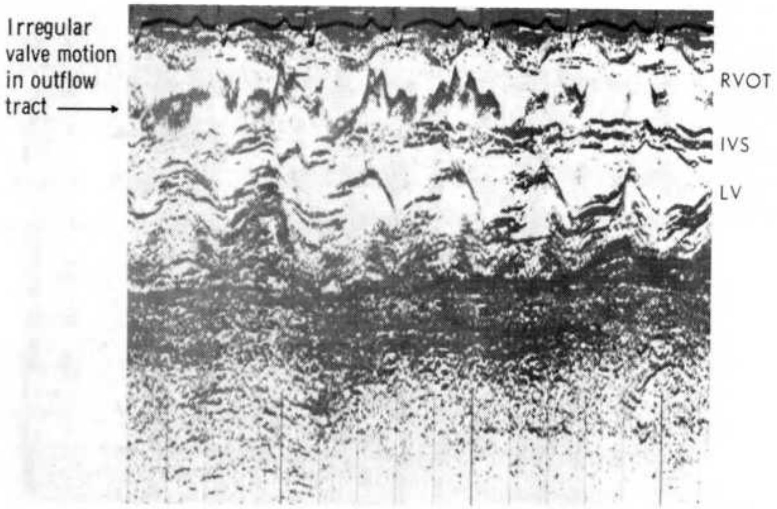

Fig. 1 *Preoperative echocardiogram. Irregular valve motion is seen in the right ventricular outflow tract (RVOT) throughout the cardiac cycle. IVS, interventricular septum; LV, left ventricle.*

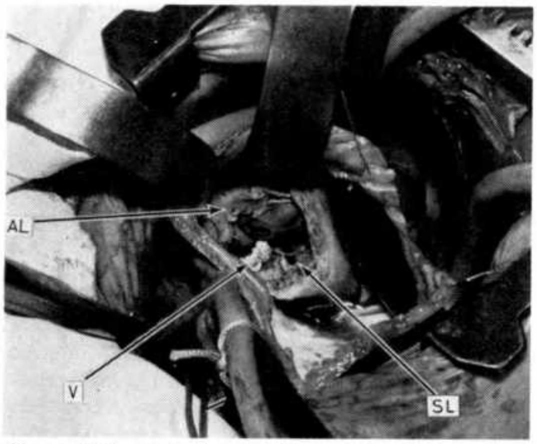

Fig. 2 *Tricuspid valve seen through right atriotomy at operation. Note encrusted vegetation (V) arising from area of ventricular septal defect and remnants of anterior leaflet (AL) of tricuspid valve. SL (septal leaflet). Posterior leaflet not seen.*

Left ventricular to right atrial communication via the tricuspid valve is well described.[4] The ventricular septal defect opens into the right ventricle behind the septal leaflet of the tricuspid valve. Whereas there is usually a second deficiency in the septal leaflet, in this case a destroyed anterior leaflet gave rise to a clinical picture dominated by acute tricuspid regurgitation, rather than a left-to-right shunt. In fact, the cardiac catheterisation disclosed a left-to-right shunt through the ventricular septal defect and a right-to-left shunt through the persistent foramen ovale. This bidirectional shunting together with the gross tricuspid regurgitation probably accounted for the mild degree of central cyanosis.

Echocardiography is being used increasingly in the study of tricuspid valve disease. It has been suggested that systolic flutter of the tricuspid valve caused by the passage of left ventricular blood into the right atrium is of value in the recognition of congenital left ventricular-right atrial communication.[5] In this case the near total destruction of the anterior leaflet and a consequently unsupported posterior leaflet resulted in a valve which was completely flail, and abnormal tricuspid valve motion was observed throughout the cardiac cycle.

We thank Dr M Tynan who performed the cardiac catheterisation.

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Br Heart J 1980; **43**: 702–4

Abnormal diastolic motion of interventricular septum during inspiratory phase

Echocardiographic study

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SUMMARY We report on a patient without heart disease who had pulsus paradoxus, associated with echocardiographic evidence of abnormal and exaggerated diastolic motion of interventricular septum. Both phenomena appeared at the peak of the inspiratory phase of respiration, and seemed to be produced from the same haemodynamic variations, of which the echocardiographic pattern appears to be a more sensitive index than the sphygmographic one.

Echocardiography has made possible the study of interventricular septal motion. Using this method, it has been shown that the interventricular septum presents abnormalities, both in direction and extent of movement, as a result of pathological change or because of exaggerated physiological variations.[1] It is known that, particularly in young people, the interventricular septum can show a periodic displacement with the different phases of respiration.[2]

To our knowledge, no case of abnormal diastolic motion of the interventricular septum, related to the peak of inspiration and as exaggerated as in our patient, has been reported in a subject without heart disease.

Case report

A 53-year-old man without any significant complaint was seen as an outpatient. The electrocardiogram was normal; and the chest *x*-ray films were also normal, except for evidence of moderate pulmonary emphysema which was confirmed by pulmonary function tests. Phonomechanographic examination showed a reduction in peripheral pulse amplitude during inspiration. The subject was normal in every other respect.

The echogram showed no alteration, except for an abnormal motion of the interventricular septum at the peak of inspiration (Fig. 1).

A reduction in arterial pulse amplitude was observed in every first beat after the abnormal septal motion (Fig. 2).

The average values of systolic and diastolic dimensions of the ventricles, both in inspiratory and expiratory phases, are reported in the Table.

It is apparent that at the peak of inspiration the right ventricular diastolic dimension was larger than in expiration, so that it was equal to the left ventricular diastolic dimension.

In the left ventricle, during inspiration, the usual systolic shortening of the internal transverse diameter was almost absent. But such systolic shortening was unusually high in the right ventricle in the same respiratory phase. It appeared to be dependent on the abnormal diastolic septal motion.

Discussion

The exaggerated paradoxical septal motion in this case was clearly connected to the phases of respiration. It appeared exclusively at the peak of inspiration, namely whenever intrathoracic negative pressure reached its maximum. It seems justifiable

Table *Average values (mm) of right and left ventricular internal diameters (RVID and LVID) in systole and diastole and during inspiratory and expiratory phases*

		Inspiration	*Expiration*
RVID	Diastole	46	29
	Systole	24	24
LVID	Diastole	38	55
	Systole	42	40

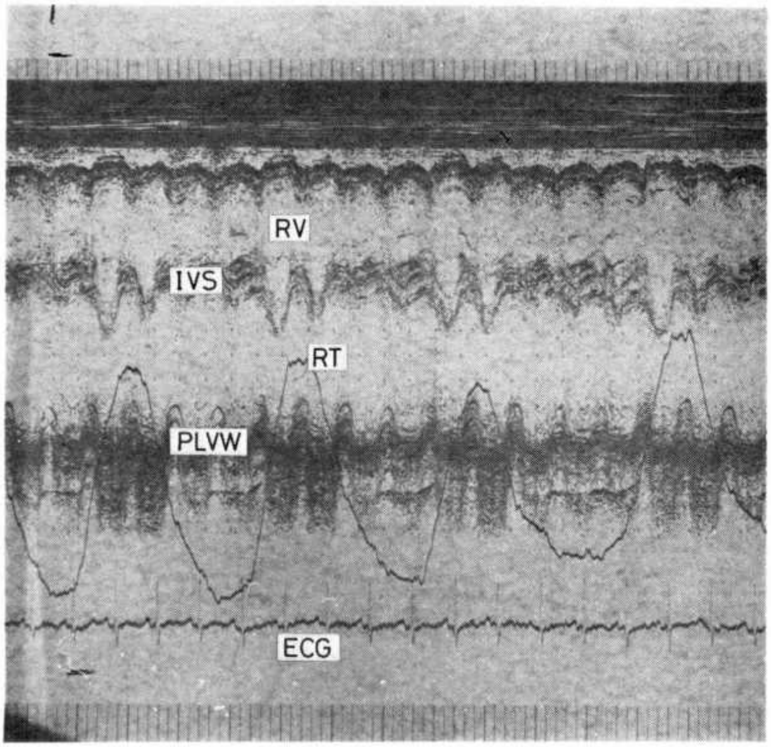

Fig. 1 *Right and left ventricle M-mode echogram. Paper speed: 10 mm/s. Respiratory tracing is recorded. Abnormal septal movements are observed at the peak of inspiratory phases. RV, right ventricle; IVS, interventricular septum; RT, respiratory tracing; PLVW, posterior left ventricular wall; ECG, electrocardiogram*

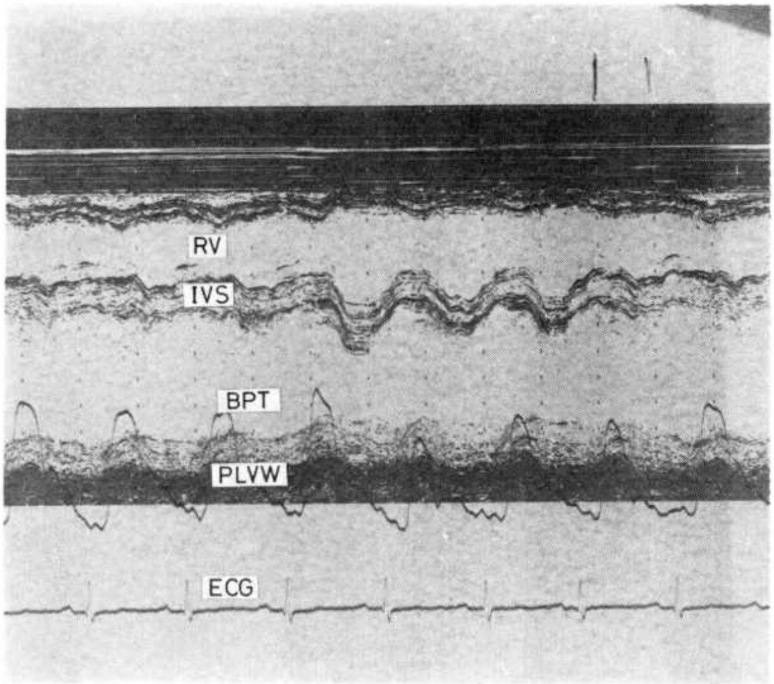

Fig. 2 *Right and left ventricle M-mode echogram. Paper speed: 25 mm/s. Recording of right brachial external pulse tracing. A reduction in pulse amplitude is evident in the first beat after abnormal septal motion. BPT, brachial pulse tracing; other abbreviations as in Fig. 1.*

to suppose that the abnormal septal motion was a consequence of haemodynamic variations produced from the lowering of intrathoracic pressure. Such a lowering might be unusually pronounced in our patient, because of his pulmonary emphysema.

During inspiration, right ventricular diastolic filling increased conspicuously, while left ventricular diastolic filling was reduced; consequently, an abnormal septal motion appeared. Therefore, the negative intrathoracic pressure, while increasing the systemic venous return, also leads to increased pooling of blood in the lungs, so reducing left ventricular preload.[3 4] (Systemic venous return is further enhanced by abdominal venous compression as the diaphragm descends.)

In Fig. 2 echocardiographic evidence of paradoxical septal motion is more apparent than the sphygmographic pattern of pulsus paradoxus, with the implication that the former appears to be a more sensitive index of haemodynamic variations which are able to produce both phenomena.

In the present study we showed that the reduction in pulse amplitude was relatively small, and, since the transverse left ventricle diameter did not show variation in systolic shortening, it seems likely that the stroke volume was preserved by the shortening of the left ventricular diameters other than transverse.

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Br Heart J 1980; **43**: 705–8

Left main stem coronary artery dissection

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SUMMARY Left main stem coronary artery dissection is a rare cause of sudden death. This occurred in a previously asymptomatic 42-year-old white woman; clinical, arteriographic, and necropsy findings are described. Extrathoracic total body perfusion with isolated catheter perfusion of the dissected coronary artery using cold cardioplegic solution may be effective preoperative treatment.

Spontaneous dissection of the coronary arteries is a rare cause of death occurring predominantly in previously asymptomatic young women, often in the puerperium.[1] Cases of coronary artery dissection (both acute and delayed) have been recognised in association with coronary angiography; these patients probably have the best chance of survival as the condition can be readily recognised in the catheter laboratory or shortly after the investigation.[2] It has been described as a complication of cardiac operations,[3] and related by these authors to postoperative increases of systolic blood pressure or trauma to the coronary orifices by prosthetic valve cages or coronary cannulae. Most cases of coronary artery dissection involve the anterior descending branch of the left coronary artery. Left main stem dissection has been previously described in two cases only.[4 5]

Case report

A white woman aged 42 had had four uneventful pregnancies, the last one eight years previously, and gave a history of migraine which had been treated with low dose clonidine (Dixarit).* She had no recent treatment, was a mild smoker (three a day), and was not taking oral contraceptives. Her husband, a medical practitioner, had noted in the past random blood pressures of 90 to 110/65 to 70 mmHg.

At 9.30 am after a leisurely breakfast, she complained of a tight feeling in the chest which rapidly escalated into a severe, crushing retrosternal pain. She became hypotensive, sweaty, and syncopal. She was transferred immediately to Dunedin Hospital where on admission she was conscious, rational, and anxious. Blood pressure was 90/60 mmHg. An electrocardiogram taken at admission showed an intraventricular conduction defect. On transfer to the medical intensive care unit she developed bradycardia, which responded to atropine, followed by sinus tachycardia. Ventricular fibrillation occurred which was unresponsive to countershock. Cardiac massage was initiated with the Automatic Resuscitator,† maintaining cardiac output, consciousness, and urinary output. Diagnoses considered were pulmonary embolus, myocardial infarction, and aortic dissection.

She was transferred to the catheter laboratory for right and left heart studies while still being mechanically massaged. A systolic pressure of 60 mmHg was maintained throughout all chambers by the mechanical resuscitator. Pulmonary angiography showed normal pulmonary arteries. For left coronary arteriography resuscitation was temporarily stopped, so that during this time there was no effective cardiac output. After injection (5 s) massage was resumed. Fig. 1 shows the contrast in the left main stem and shows the dissection spreading to the origins of the circumflex and anterior descending branches. No pressure was recorded with the catheter passed through the coronary lumen showing that obstruction was complete. There was no subsequent clearing of the contrast medium.

As there seemed no other prospect of restoring cardiac action, operation was undertaken. Massage continued while femoral vein femoral arterial by-

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*Boehringer Ingelheim, PO Box 23-651, Auckland ,New Zealand.

†M.I.I. Life Aide Cardiopulmonary Resuscitator, Michigan Instruments Inc., 305 W. Fulban Street, Grand Rapids, Michigan 49504, Michigan, USA.

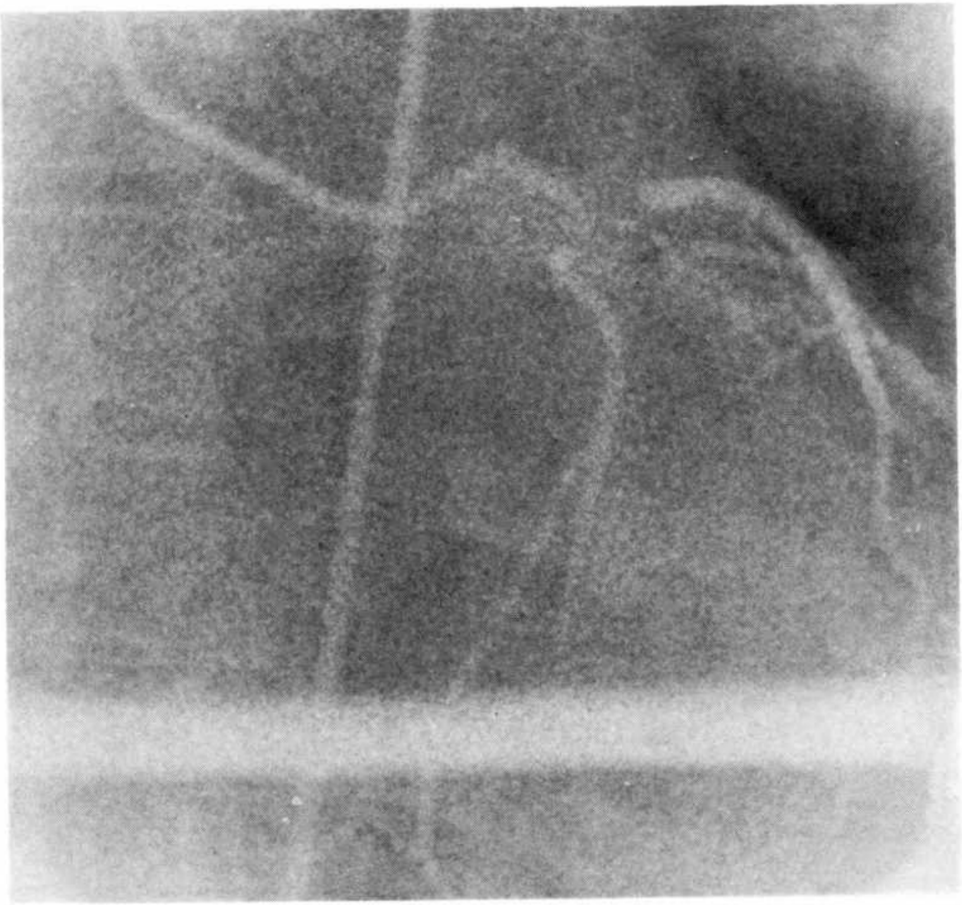

Fig. 1 *The left coronary angiogram. Contrast outlines the dissection at the origin of the circumflex and anterior descending arteries. The solid bar is the support of the mechanical resuscitator.*

pass was instituted. A flow of 3·3 litres per minute was obtained and hypothermia to 28°C was rapidly achieved. The massage was discontinued, the chest rapidly opened, and perfusion converted to bicaval femoral artery bypass. Local cooling with normal saline at 4°C was started. The aorta was cross-clamped and hypothermic (4°C) cardioplegic solution* instilled into the aortic root. On initial inspection the right ventricle was fibrillating and the left ventricle exhibited the 'stone heart' phenomenon.[6] There was no evidence of dissection on the external surface of the heart. Saphenous vein bypass grafts were attached rapidly to the obtuse marginal and anterior descending coronary arteries. It was noted that a probe in the anterior descending artery readily passed retrogradely into the aorta. The heart defibrillated spontaneously on rewarming but it quickly became obvious that the right ventricle only was contracting. Intra-aortic balloon pumping was instituted but restoration of effective left ventricular contraction was not achieved. It was clear that the ischaemic infarct of the left ventricle had been converted into a haemorrhagic infarct.[7]

PATHOLOGY

The abnormal findings were confined to the heart which was of normal size (250 g). The grafts were patent. There was full thickness haemorrhagic infarction of the entire free wall of the left ventricle and the anterior third of the ventricular septum. The region infarcted was that supplied by the left coronary artery. The coronary arteries arose normally from the aorta. The main stem of the left coronary artery trifurcated giving rise to a large anterior descending branch, a moderate sized circumflex branch, and a small diagonal branch. An intramural dissection (Fig. 2) involved the left main stem for 1·5 cm, the anterior descending and diagonal branches for a distance of 1 cm from their origins, and the circumflex for 1·5 cm. A small intimal tear was identified in the left main stem artery near its trifurcation. The dissection extended one-quarter to two-thirds of the circumference of these vessels and was located in the outer media. The false channel contained both clotted and unclotted blood. The right coronary artery was the dominant arterial vessel to the inferior surface of the heart. This artery appeared macroscopically normal with a smooth intimal surface, but histologically there was diffuse intimal thickening, with irregular elastic laminae and abundant smooth muscle cells but without significant fibrosis or lipid deposition. The arterial media contained sparsely scattered pools of mucopolysaccharide material (Fig. 3) which stained positively with alcian blue. These ground substance accumulations were present where the right coronary artery had a muscular media, yet were not observed in the aorta and proximal coronary arteries, both of which had an elastic media. Other small muscular arteries throughout the body were normal. Similar medial pathology was present in the left coronary artery, though this was obscured by the dissection.

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* *Composition of aortic root perfusate*
Sodium, 157 mmol/l; potassium, 14·2 mmol/l; magnesium, 2·63 mmol/l; chloride, 99·1 mmol/l; acetate, 23·6 mmol/l; gluconate, 20·1 mmol/l; bicarbonate, 35·0 mmol/l; dextrose, 43·8 g/l. Osmolality 656 mosmol/l. Isolyte S supplied by: McGaw Laboratories, Glendate, California 91201, USA.

Discussion

This catastrophic cause of sudden death was well described by Malloch[1] who reviewed 34 published cases. One of these patients may have had a traumatic dissection as there was a history of a kick on the chest by a horse. Their ages ranged from 21 to 62 years (mean of 41·5 years); only four patients were older than 50. Twenty-six were women, 10 being recently *post partum*. Only two patients had left main stem dissection; in 27, the dissection involved the anterior descending artery, in four the right coronary artery or its branches, and in one the circumflex artery.[1, 5] Twenty-four patients died

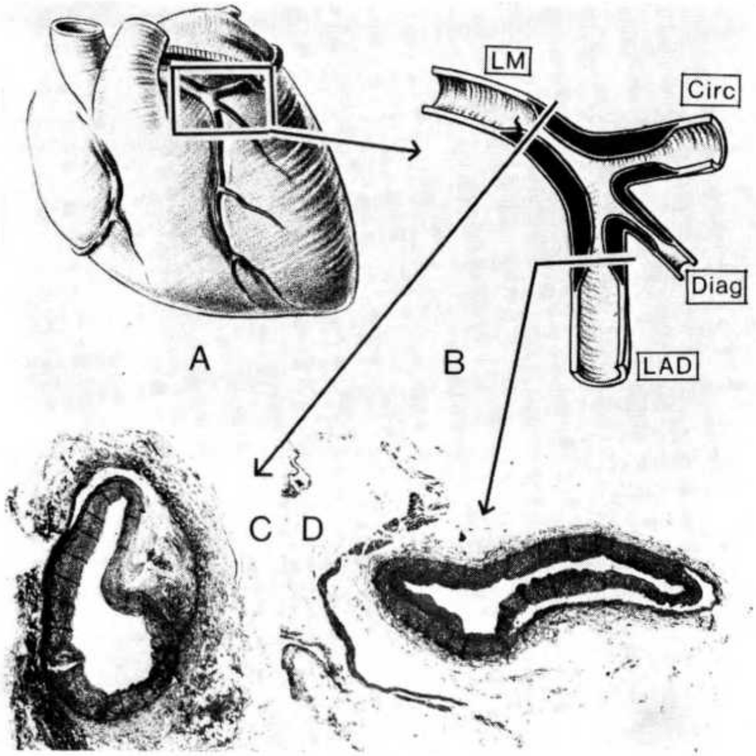

Fig. 2 (A) *Diagram of the anterior surface of the heart.* (B) *Enlarged view of the trifurcation showing the extent of the dissection process in the left coronary artery.* (C) *and* (D) *Histological sections of the left main stem coronary artery and anterior descending branch, respectively. The false channel of the left main stem is partially filled with fibrin clot. (Elastic van Gieson. Original magnification × 15 and × 25, respectively.)*

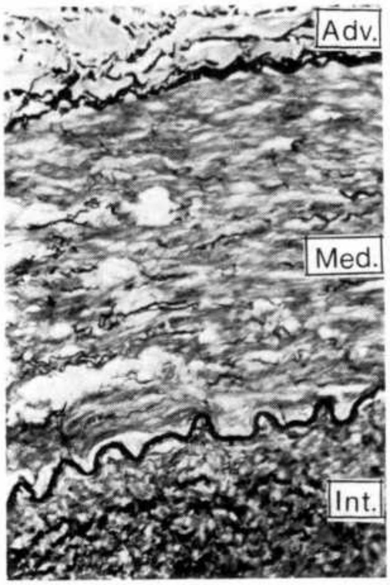

Fig. 3 *Histological section of the right coronary artery. Several pools (cysts) of mucopolysaccharide ground substance are present in the arterial media. Moderate musculoelastic intimal thickening is also shown. (Adv., adventitia; Med., media; Int., intima) (Elastic van Gierson. Original magnification × 300.)*

suddenly, six patients survived with myocardial infarction, and the outcome was not stated in the other four. Little information was given about the state of the vessels involved: three had doubtful cystic medionecrosis, one medial degeneration, two whorl formation in the media, and two intimal tears, but the histology was not stated in the remainder. The association with the puerperium is unexplained. Hypertension did not seem to be a causative factor as is the case with aortic dissection.

In our patient the coronary arteries showed intimal thickening and mild 'cystic' change in the media. The intimal thickening diffusely involved the proximal portions of both vessels, but did not resemble atherosclerosis and was composed of smooth muscle cells with elastic fibrils. The medial change was characterised by mucopolysaccharide pools ('cysts') and involved both coronary arteries. It is of particular note that the aortic media, where this type of medial pathology is more frequently encountered, was histologically normal.

The diagnosis should be suspected in the young woman with no antecedent history who presents with severe unexpected circulatory collapse especially if the event is related to the puerperium. Because of the rapid course of the catastrophic illness the clinician often has little chance of applying effective treatment. If, however, the diagnosis is suspected, immediate coronary angiography can be performed even if mechanical massage is in progress. Then, if the diagnosis is confirmed, the catheter could be passed beyond the dissection and infusion of hypothermic cardioplegic solution started. Cardiopulmonary bypass can be started via the femoral vein and femoral artery providing organ perfusion before the induction of anaesthesia, while coronary perfusion should protect ischaemic myocardium by substrate provision and hypothermia. The danger of extraluminal penetration exists, but this risk must be accepted in a potentially lethal situation. This approach may offer the patient some hope of survival if such an event occurs in a hospital with cardiac surgical services.

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Br Heart J 1980; **43:** 709–11

Sudden death during marathon racing: hyperpyrexia versus myocardial ischaemia

Sir,
The report from South Africa[1] asserts that an experienced marathon runner with hypertrophic cardiomyopathy died from myocardial "ischaemia", collapsing near the 20 mile mark in a race. The "naked eye" necropsy showed no cause of death. The coronary arteries were normal. They support their diagnosis of "ischaemia" with a low potassium/sodium ratio in the myocardium. However, this low ion ratio only indicates injury, probably caused by ventricular fibrillation.[2] The specific term "ischaemia" should be limited to those cases with significant coronary artery disease.

We maintain worldwide, forensic surveillance over marathon runners,[3] and have encountered similar cases. Fatal and nonfatal arrhythmias have occurred during racing in association with exertion-induced heat illness, dehydration, pyrexial illness, and the consumption of drugs. It is unfortunate that Noakes *et al.* were limited to the examination of a single, autolysed organ, the heart. The Figure showed complete loss of myofibril nuclear detail, suggesting that death occurred during hyperpyrexia, and refrigeration was not available during the 48-hour delay before necropsy. Timely microscopical studies could have ruled out viral infection. Chemical tests for alcohol, caffeine, and other drugs should have been performed in view of the negative "naked eye" necropsy. Knowledge of racing conditions helps evaluate the possibility of heat stress and dehydration. These basic forensic steps would have added greatly to the value of their report.

The use of the term "ischaemia" instead of "heat injury" in these cases suggests an increased hazard of road racing. Appropriate safety precautions cannot be taken until the true dangers are known. In addition, the treatment for collapse resulting from heat stroke is different from the treatment for ischaemic heart disease. To delay cooling measures can be fatal.

Other reports from South Africa have confused the effects of racing hyperpyrexia with "ischaemic heart disease".[4] Our own surveillance has uncovered similar iregularities among the reports of Noakes *et al.*[5] When a 19-year-old died during a marathon, Opie[6] reported that coronary "atheroma" was the cause of death; however, the necropsy showed "normal" coronary arteries.[7] When a 35-year-old marathon runner died after taking long training runs, Opie[6] reported that the *necropsy* showed "ischaemic heart disease with a number of small infarcts". However, there was *no* necropsy,[7] and the electrocardiogram was consistent with heat stroke.[8] We believe that this confusion delays any efforts at improving racing conditions.

Noakes *et al.* chastise the stricken runner because he "chose to ignore his symptoms and to conceal these from his doctors". They caution that "symptoms suggestive of myocardial ischaemia must be investigated". Their previous report suggests otherwise. When six runners developed exertional symptoms,[9] all four who refused to remain in hospital survived. The single death occurred in hospital where no treatment for heat stroke was given. This runner had been taking long training runs up to 40 miles during the hot "surfing season" when symptoms appeared. His electrocardiogram suggested heat illness,[8] but he was treated for "ischaemic" heart disease. We suggest that inappropriate medical care will not improve the survival of these runners, and we excuse any South African marathon runner who elects to avoid doctors under these conditions.

We disagree with the authors' two conclusions: that marathon running "precipitated ischaemia" and "contributed to the cardiomyopathy". There is nothing in their report to support their views. By emphasising the cardiomyopathy they have missed the very real hazard of marathon running itself, namely exertion-induced heat illness.

Thomas J Bassler,
Centinela Hospital,
Inglewood, California 90307, USA.

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This letter was shown to Drs Noakes and Opie who reply as follows:

Dr Bassler has done much to promote the cause of marathon running, and we thank him for the opportunity to respond to the views in his letter.

(1) *Our case report*

That our marathon runner with hypertrophic cardiomyopathy also had ischaemic chest pain seems very probable on the history. Therefore, it seems reasonable to suggest that the runner died from myocardial ischaemia. The term "myocardial ischaemia" *can* certainly be used in the absence of coronary artery disease, for example in patients with aortic stenosis and angina.[1] In our patient the massive left ventricular hypertrophy and the anginal pain precipitated by effort and emotion indicate myocardial ischaemia, even without the tissue K^+/Na^+ values. There was no pathological evidence of autolysis as the body had been refrigerated shortly after death.

Exercise, especially if severe, is usually held to be contraindicated in patients with hypertrophic cardiomyopathy. It would be surprising if the severe exercise of marathon running could be held to have been beneficial for our patient.

(2) *Hyperpyrexia versus ischaemic heart disease*

Dr Bassler contends that South African doctors are unable to distinguish between hyperpyrexia and ischaemic heart disease and that he would "excuse any South African marathon runner who elects to avoid doctors under these conditions". In support of this statement he supplies a series of half-truths. The facts of the matter are the following:

(i) that South African researchers were among the first to draw attention to the dangers of hyperpyrexia in marathon running[2];

(ii) that one of the present authors (TDN) has written extensively in both the medical[3] and lay journals[4] regarding the dangers and preventable aspects of marathon and ultra-marathon running in a hot environment like that of South Africa;

(iii) that despite similar environmental conditions, hyperpyrexia and heatstroke in runners appear to be more of a problem in North America[5, 6] than in South Africa;

(iv) that the 35-year-old marathon runner who was admitted to hospital and subsequently died, did *not* die from heatstroke. Our preliminary erroneous letter that there was a necropsy has been corrected on numerous occasions.[7–9] Heatstroke could not explain the abnormal electrocardiogram of this patient who had not run at all on the day of his death, but had been in the sea, surfing—a combination of circumstances totally excluding heat injury. The patient suffered from repetitive exertional chest pain; during one 4½ mile time trial his wife recalls that the patient was forced to stop running four to five times.[7, 9] Such anginal pain is a feature of ischaemic heart disease, not of heatstroke. By repeatedly and incorrectly presenting this case as an example of heatstroke on the basis of an erroneous interpretation of the electrocardiogram,[10] Dr Bassler destroys the force of his arguments. It is difficult to see how treating a fully lucid man (a finding which by itself excludes a diagnosis of heatstroke), who has just been surfing, for heatstroke, and ignoring his severe praecordial chest pain would be medically justifiable;

(v) that though the delayed cooling of a patient with heatstroke may indeed be fatal, the correct treatment for the apnoeic patient who dies suddenly during marathon running, as did our patient with cardiomyopathy, is cardiopulmonary resuscitation and not cooling; and

(vi) that there is as yet no published evidence showing that electrocardiographic abnormalities in marathon runners can be explained on the basis of hyperpyrexia nor that heatstroke can present as instantaneous exercise-related death.[9, 11]

Dr Bassler's contention that four of our runners with myocardial infarction refused to remain in hospital is an understandable misinterpretation of ambiguities in our 1977 paper.[7] Though one patient refused admission to hospital, none of the other patients refused to stay in hospital, but were discharged normally by their physicians. In the days immediately after their discharge from hospital, however, three patients began walking and jogging again. It was this early return to an exercise training programme which they had been advised against by their physicians. We apologise for these ambiguities in our earlier paper.

We eagerly await Dr Bassler's detailed publications refuting these statements and look forward to reading his other, as yet unpublished, studies showing that death in marathon racing is more likely to be a result of viral infection, alcohol, caffeine, and other drugs than to myocardial or coronary artery disease. We are grateful that he did not accuse us of failing to determine whether the runner's diet was inadequate in yeast, yogurt, peanuts, beer, wheat germ, or vitamin C as a dietary deficiency of any one of these is also held by Dr Bassler to be a cause of sudden death in marathon runners.[12] Athletes who die suddenly during marathon races are more likely to die from necropsy-proven diagnoses such as myocardial disease or coronary artery disease[8] than from the other obscure reasons Dr Bassler gives.

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Groote Schuur Hospital and
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South Africa.

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Br Heart J 1980; **43**: 712

Ischaemic heart disease in young hypertensive women

Sir,
The authors of this paper (*Br Heart J* 1980; **43**: 80–7) do not appear to differentiate between ST and T wave abnormalities confined to the lateral leads and those found in other leads. It is therefore possible that in some of their cases the repolarisation abnormalities which they observed may have been a result of left ventricular hypertrophy rather than of ischaemic heart disease.

It is not sufficiently recognised that ST and T wave abnormalities resembling those of myocardial ischaemia and without increased R and S wave voltage may be found in patients with "pure" left ventricular hypertrophy, that is patients who give no history of angina and show no abnormality on coronary arteriography.

David Short,
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Aberdeen Royal Infirmary,
Foresterhill,
Aberdeen AB9 2ZB.

This letter was shown to Dr Mackay and his co-authors who reply as follows.

Sir,
Dr Short is correct in expressing concern about the specificity of electrocardiographic findings supposed to indicate myocardial ischaemia; we share some of his concern. We agree that ST segment and T wave changes occurring in left ventricular hypertrophy and strain are difficult to distinguish from ST and T wave changes occurring, in the same leads sometimes, in ischaemia without left ventricular hypertrophy. Evidence that the former is not ischaemic is scanty. We also recognise, and discuss in our paper, the occurrence of ST and T changes without evidence of coronary disease, and the occurrence of coronary disease without ST and T wave changes.

Our main case rests, not with ST segment and T wave changes on the electrocardiogram, but with angina pectoris and the clinical manifestations of ischaemic heart disease; 22 per cent of the young women in our series of patients with diastolic blood pressures of 120 mmHg or more had a clear history of angina pectoris.

A Mackay, A M M Cumming,
J J Brown, A F Lever,
J I S Robertson,
MRC Blood Pressure Unit,
Western Infirmary,
Glasgow G11 6NT.

Br Heart J 1980; **43:** 713

Transient early diastolic murmur and end stage renal disease

Sir,
A transient early diastolic murmur may be heard in patients with end stage renal disease. This was initially attributed to aortic regurgitation secondary to fluid overload.[1] This view was supported by Alexander and Polak,[2] who described the appearance of the murmur in seven patients with end stage renal failure during episodes of fluid overload; their description of the murmur supports their conclusions that it was of aortic origin.

We have, however, had a patient in end stage renal failure in whom an early diastolic murmur was associated with episodes of typical pericardial pain while he was salt and water depleted. The murmur was loudest when he lay supine and it was clearly audible all over the praecordium. We believe that this observation supports the hypothesis of Barrett *et al.*[3] that an early diastolic "murmur" may be a pericardial noise indicative of uraemic pericarditis. This possibility was not mentioned by Alexander and Polak.

Barrett described eight patients and commented that the murmur was not typical of aortic regurgitation in that it was maximal in intensity at and localised to the cardiac apex and became softer when the patient leaned forward. Aortography in six of the patients identified only one patient with possible aortic regurgitation, while echocardiography showed that in all five patients examined a posterior pericardial effusion was present. They concluded that "the early diastolic murmur of renal failure does not usually arise from functional aortic incompetence but may be a sound of pericardial origin". Barrett's conclusions are not supported by Storstein and Örjavik.[4] They found that in a group of 21 patients with advanced renal failure in whom a diastolic decrescendo murmur was heard, eight had evidence of organic aortic regurgitation and six of the remaining 13 had aortograms which showed that four had aortic regurgitation which was probably functional.

The origin of the early diastolic murmur associated with renal failure is therefore still in doubt. It is possible that it is related to functional aortic regurgitation in some patients and to uraemic pericarditis in others. It is important to identify cases of pericarditis at an early stage since it is an indication for urgent dialysis and a contraindication to anticoagulation because of the dangers of cardiac tamponade. It is possible that a pericardial friction rub may be mistaken for an aortic early diastolic murmur. When an early diastolic murmur is observed in chronic renal failure, the possibility that it is pericardial in origin should be considered, especially if it is not typical of aortic regurgitation.

Malcolm VandenBurg,
Rodney Foale,
The London Hospital,
(Whitechapel).

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This letter was shown to Dr Alexander and Professor Polak who comment as follows.

Sir,
We agree that there may be occasions when a pericardial friction rub mimics an aortic diastolic murmur, and this should be suspected particularly if a patient with renal failure is salt and water depleted (our patients with functional aortic regurgitation were all overloaded with salt and water). The dilemma about heparinising the patient, however, is unlikely to arise often, and we believe that these patients can safely be heparinised if there is no clinical evidence of pericarditis other than a murmur confined to early diastole and heard best at the aortic area. Echocardiography may disclose the presence of pericardial fluid in patients with advanced renal failure, but will not resolve the dilemma.[1] We feel sure that Drs VandenBurg and Foale would agree that aortography should be reserved for the rare patient with renal failure whose murmur persists after overhydration has been corrected.

W D Alexander,
A Polak,
Saint Mary's Hospital,
Portsmouth.

Reference

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Br Heart J 1980; **43**: 714

Treatment of hypertrophic obstructive cardiomyopathy with verapamil

Sir,
We read the article by Kaltenbach *et al.*[1] with interest.

The principle of the treatment is based on the interference with calcium availability in the supernormal contracting ventricle of hypertrophic cardiomyopathy. Though the idea is appealing and the reported results impressive there is a potential problem in the use of verapamil.

Haemodynamic studies with verapamil[2] have shown a rise in the left ventricular end-diastolic pressure and a concomitant drop in dP/dt, evidence for a depressant effect of the drug on myocardial function. Such an action would be of benefit to subjects with hypertrophic cardiomyopathy.

A more recent report,[3] however, showed clearly that, because of the potent vasodilator effect of the drug, cardiac output increases, despite the decreased contractility.

In patients with hypertrophic cardiomyopathy, the pronounced vasodilator effect of verapamil could increase the intraventricular obstruction, thereby precipitating a potentially dangerous situation. It is of interest that the authors found that left ventricular pressure gradients did not show the same consistent improvement as did subjective symptoms. In some of their patients the gradients, in fact, increased after verapamil.

This potential problem should certainly be considered when using this drug in these patients.

I L Geft,
M M Zion,
Cardiology Department,
Shaare-Zedek Medical Center,
Jerusalem, Israel.

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This letter was shown to Dr Kaltenbach and Dr Hopf who reply as follows:

Sir,
Calcium antagonists have actions on the smooth muscle of blood vessels as well as on the myocardium. With different substances either the central or the peripheral effect may be more pronounced. The vasodilator activity of verapamil can best be seen after intravenous administration as a bolus injection. Theoretically, patients with hypertrophic cardiomyopathy may be made worse by this effect. In fact, however, after 10 mg verapamil intravenously there was no change in intraventricular gradient. On the other hand, after giving the substance as intravenous infusion, Rosing *et al.*[1] found, in patients with hypertrophic cardiomyopathy, a significant decrease in the intraventricular gradient from a mean of 85 to 50 mmHg, as well as a decrease in the gradient provoked by the Valsalva manoeuvre or amyl nitrite.

Our own studies with verapamil administered orally into the coronary circulation show negative inotropic and chronotropic activity. The changes seen after high-dose oral administration are comparable to the intracoronary administration.

Thus the vasodilator activity of verapamil after oral administration seems not to counteract the therapeutic benefit on the myocardium. It is, however, important to note that the beneficial therapeutic activity of this substance seen in patients with hypertrophic cardiomyopathy, therefore, can only be attributed to verapamil and not necessarily to other calcium antagonistic substances.

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Reference

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Br Heart J 1980; **43:** 715–6

The Remler ambulatory blood pressure recording system
Accuracy and reliability

Sir,
A recent letter to the editor of the *British Heart Journal* by Beevers and his co-workers presents data concerning the accuracy and reliability of the Remler ambulatory blood pressure recording system.[1] We would like to summarise our extensive experience with the Remler equipment[2] and to conjecture about possible causes for the distinct differences in our findings.

We should first point out that the letter by Beevers *et al.* deals with a more recently marketed system than the one we have tested. The two systems are, however, identical with respect to the critical components and the fundamental method of measurement.

The data presented by Beevers *et al.* suggest that the Remler system yields higher pressures than comparison instruments. Using a simple method of making simultaneous, ipsilateral measurements (a y-shaped tube connecting the arm cuff with a conventional mercury sphygmomanometer and the recorder), we collected data for a single pressure cycle in each of 100 consecutive hypertensive patients. Combining systolic and diastolic (phase V) measurements, we found agreement within 2 mmHg in 99·5 per cent of the 200 pairs of observations and identical values in 84 per cent (Table). Our mean differences (recorder minus sphygmomanometer) were 0·1 and 0·2 mmHg for systolic and diastolic pressure, respectively, as opposed to the corresponding differences of 7·4 and 10·4 mmHg found by Beevers *et al.*[1] using the same technique with a London School of Hygiene sphygmomanometer.

Table *Frequency distribution of absolute differences between simultaneous blood pressure measurements by Remler M-109 recorder and conventional mercury sphygmomanometer: one systolic-diastolic (phase V) pair in each of 100 consecutive hypertensive patients*

Difference (mmHg)	*Systolic*	*Diastolic*	*Combined*	*Combined per cent*
0	85	83	168	84·0
2	15	16	31	15·5
4	0	1	1	0·5
Total	100	100	200	100·0

Assuming that we are correct in our assertion that the minor differences between our recorders and those used by Beevers *et al.* could not account for the major differences in our findings with respect to the accuracy of the Remler system, we can only raise some questions about the possibility that Beevers's laboratory was using an incorrect decoding technique and/or defective equipment. Both these conjectures seem plausible in the light of statements by Beevers *et al.* that only 50 per cent of their home blood pressure readings "could be interpreted from the print-outs" and that the "most frequent reason for inability to obtain readings resulted from calibration artefacts obscuring the pulse beats . . ."

The "ability to obtain readings" does not principally depend on the legibility of the ink-pen record. Accurate measurements with the Remler system primarily require careful aural tape-monitoring and can be readily achieved without optimal chart recordings. One of the major strengths of the Remler design is that it does not electronically "interpret" Korotkoff sounds or arterial movements. Instead, it provides a direct analogue to the conventional auscultatory method, thereby making possible the close agreement we have found between the two sources of measurements.

"Calibration artefacts" in Remler recordings are usually attributable to drained batteries, a broken cable, or a dirty transducer assembly. If the recorder is routinely maintained and tested before each ambulatory study, the failure rate can be kept within an acceptable range. Our own laboratory has processed more than 50 000 hours of blood pressure recordings made with Remler equipment; we estimate that we successfully measure 90 to 95 per cent of the readings. Certainly, any recorder in our laboratory that showed a 50 per cent failure rate, even on a single occasion, would immediately be checked to identify the cause of the malfunction.

Ronald Cowan,
Maurice Sokolow,
Dorothee Perloff,
Computer Center,
Department of Medicine, and
Cardiovascular Research Institute,
University of California,
San Francisco, California 94143,
USA.

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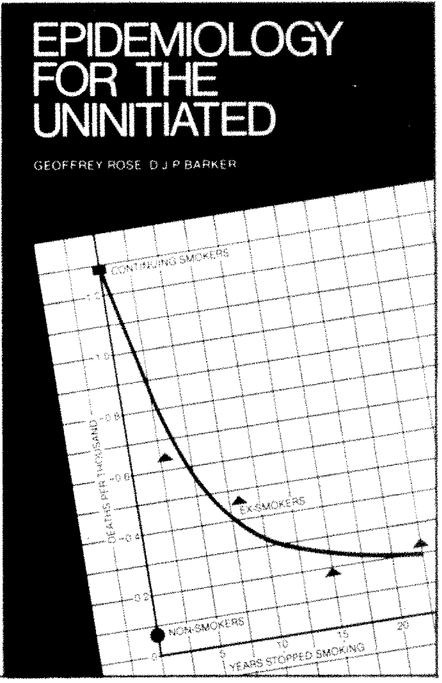

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Br Heart J 1980; **43:** 717–727

Proceedings of the British Cardiac Society

THE 59TH ANNUAL GENERAL MEETING of the British Cardiac Society was held at the Royal Free Hospital, London on Wednesday and Thursday, 23 and 24 April 1980. The President, W SOMERVILLE, took the Chair during private business. At the scientific sessions the Chair was taken by CECIL SYMONS.

Abstracts of papers

Influence of changing antiarrhythmic drug policy on incidence and outcome of ventricular fibrillation complicating myocardial infarction

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P J Cadigan, K L Evemy, E J Flint
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Birmingham 4

We have assessed the effect of a progressive reduction in the use of antiarrhythmic drugs in the management of acute myocardial infarction over a 12-year period.

A total of 1481 patients were admitted to a coronary care unit during the three periods, 1967–8, 1972–3, and 1977–8. The age and sex distribution of the patient population remained constant. In 1967–8, 40 per cent of patients received intravenous lignocaine or alternative antiarrhythmic treatment, with only 21 per cent in 1972–3 and 10 per cent in 1977–8. The indication for antiarrhythmic drug treatment in 1967–8 was the presence of ventricular ectopic activity in 70 per cent of cases, whereas in 1977–8 the indication for treatment was a preceding episode of ventricular fibrillation in all but 35 per cent. The incidence of ventricular fibrillation occurring within the unit during the three periods under review was 13, 10, and 10 per cent, respectively. Direct current countershock resulted in restoration of spontaneous heart rhythm in 80 to 85 per cent of all patients, but only 39 per cent survived hospital admission in 1967–8, 55 per cent in 1972–3, and 50 per cent in 1977–8. Death after an initially successful resuscitation was almost invariably the result of heart failure rather than an arrhythmia. Suppression of ventricular ectopic activity by lignocaine, in the doses used at the time of the study, was of no benefit in either reducing the incidence of ventricular fibrillation or altering its outcome.

Comparison between oral mexiletine, disopyramide, and placebo used prophylactically after acute myocardial infarction

N C Jackson, J M Metcalfe, C Wade, A McLeod,
D E Jewitt
Cardiac Department, King's College Hospital,
London SE5

The presence of ventricular premature beats on random electrocardiograms or 24-hour tape electrocardiograms is said to increase the risk of sudden cardiac death after acute myocardial infarction. Reducing or abolishing ventricular premature beats might therefore decrease the risk of sudden cardiac death. Ninety-five patients in hospital with proven acute myocardial infarction were randomly assigned to three oral, double blind treatment groups between six and 10 days after infarction. Thirty-one patients took mexiletine (600 to 750 mg/day) continuously for three months; 31 took disopyramide (300 to 600 mg/day); and 33 took placebo capsules. Twenty-four-hour electrocardiogram tapes were recorded before medication and after one, three, and four months.

The mean daily ventricular premature beat count per patient was not significantly different between the three groups either before, during, or after medication. No apparent change in mean daily ventricular premature beat frequency occurred in any group during the four months. No medication had significant effects on ventricular tachycardia or couplet frequency. Three patients in each group reinfarcted. Death occurred in five patients taking disopyramide, three taking mexiletine, and two taking placebo, only four of these being sudden coronary deaths. Side effects were common, resulting in eight patients stopping mexiletine, three stopping disopyramide, and two stopping placebo despite non-toxic plasma levels.

These results do not support the routine prophylactic use of disopyramide or mexiletine after myocardial infarction.

Failure of predischarge ambulatory electrocardiographic monitoring to predict sudden death after myocardial infarction

P J Cadigan, R E Nagle, B L Pentecost,
P Weissberg, J de Giovanni
The General Hospital, Birmingham, and
Selly Oak Hospital, Birmingham

Recent studies have suggested that frequent or complex ventricular premature beats detected in the late hospital phase of myocardial infarction may identify patients at high risk of sudden death.

We have performed 24-hour ambulatory electrocardiographic recordings on 139 survivors of myocardial infarction 48 hours before discharge from hospital to select high risk cases for inclusion in a secondary prevention study. Using the Reynolds Pathfinder system for analysis, 42 patients had frequent (>30/hour) or complex (runs of two or more consecutive) ventricular premature beats and were classified as "high risk". Ninety-seven patients had less than 30 ventricular premature beats/hour and were classified as "low risk".

During a mean follow-up period of six months seven deaths have occurred in the high risk group. Five deaths were sudden and five occurred before discharge from hospital. Seven of the 12 deaths in low risk patients were sudden.

When restudied one month after discharge 51 per cent of "low risk" patients had developed "high risk" arrhythmias.

Conclusions:
(1) 24-hour electrocardiographic recordings made immediately before discharge identified patients in immediate danger of sudden death but failed to predict long-term risk. (2) Ventricular premature beats increase in frequency after discharge from hospital.

Right ventricular outflow tachycardia: distinct clinical entity

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Pacemapping for ventricular tachycardia has allowed the recognition of the surface electrocardiographic appearances of ventricular tachycardia originating in different parts of the ventricles. When cases of idiopathic ventricular tachycardia were analysed a disproportionate number arose from the outflow tract of the right ventricle.

Epi- and endocardial pacemapping (four cases) has shown that right ventricular outflow ventricular tachycardia is characterised by left bundle-branch block pattern and inferior frontal axis (+80° to +100°).

Ten cases (five men, five women) of right ventricular outflow arrhythmias are presented, ranging from ventricular fibrillation (one case) and monoform ventricular tachycardia (seven cases) to couplets (two cases).

The patients were young (mean age 26·9 years) and the histories were short (mean 17·8 months).

The QTc in sinus rhythm was prolonged in every case (mean 0·47 for men and children, and 0·44 s for the women).

In three cases an infectious illness (mumps, varicella, and mycoplasma pericarditis) preceded the onset of ventricular tachycardia, and one case was Kveim positive. Two cases showed congestive cardiomyopathy. Other cases had no structural heart disease.

No single treatment was effective in all cases. These arrhythmias proved refractory to disopyramide in seven cases, and to amiodarone in three cases. Amiodarone was successful in two cases, oxprenolol in one case, continuous atrial overdrive pacing in one case, and dual demand right ventricular pacing in two cases. Operative right ventricular pacemapping and excision of ventricular tachycardia origin proved successful in one case.

Relation between symptoms, initiation zone, and oral antiarrhythmic treatment in re-entry atrioventricular tachycardia

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Of 43 patients with paroxysmal reciprocating atrioventricular tachycardia who had undergone intracardiac electrophysiological testing, 31 were treated successfully either with slow-channel or fast-channel antagonists or a combination. Thirty-one patients had Wolff-Parkinson-White (WPW) syndrome—concealed in 13—the remainder had intra-AV nodal tachycardia. None had documented atrial fibrillation. During the electrophysiological study the widest zone over which single atrial premature beats initiated tachycardia both during sinus rhythm and atrial pacing was measured.

The patients with concealed WPW syndrome had the widest initiation zones, exceeding 150 ms in six. These patients also tended to have the most frequent episodes of tachycardia, five had more than one per week. Successful treatment was achieved in seven, of whom five received slow-channel antagonists. The initiation zone was variable in the patients with overt pre-excitation, often related to the anterograde refractory period of the accessory pathway. In 10 the initiation zone was ⩽20 ms and five had less than four attacks per year. Thirteen were treated successfully, a combination of slow- and fast-channel antagonists being most effective (six). In two, fast-channel antagonists alone succeeded. Intranodal re-entry was characterised by a variable initiation zone and variable frequency of tachycardias. Eleven were successfully controlled and in all but one this was achieved with slow-channel antagonists.

This study demonstrates the efficacy of specific channel antagonists in a high proportion of cases and may allow prediction of success when the mechanisms have been defined, which was often possible from clinical tracings.

Arrhythmia and mortality in hypertrophic cardiomyopathy

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Retrospective analysis of 216 patients with hypertrophic cardiomyopathy, follow-up one to 23 years (mean six), disclosed that 48 had died, 24 of them suddenly. The 168 survivors were compared with the 48 who died. The following features were associated with poor prognosis: young age ($p < 0{\cdot}003$), dizziness ($p < 0{\cdot}02$), and severe dyspnoea ($p < 0{\cdot}02$) at the time of diagnosis; and cardiac surgery ($p < 0{\cdot}01$) and the onset of atrial fibrillation ($p < 0{\cdot}05$) during follow-up. Neither a positive family history nor any electrocardiographic or haemodynamic measurement predicted mortality.

Ambulatory electrocardiographic monitoring in 30 unselected patients showed that 50 per cent had multiform or paired ventricular extrasystoles or ventricular tachycardia and 46 per cent had important supraventricular arrhythmias. Neither beta-adrenergic blocking treatment nor calcium antagonist treatment with verapamil (480 mg/day) reduced the incidence of arrhythmia.

Death in hypertrophic cardiomyopathy is most often sudden. Serious albeit asymptomatic arrhythmias are frequent: a trial of two conventional treatments showed that neither was effective. The detection of arrhythmia and its effective treatment may improve prognosis in this disease.

Regional variations in cardiovascular disease in Great Britain and prevalence of risk factors

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The British Regional Heart Study aims at determining the factors responsible for the pronounced tregional variations in cardiovascular disease. Twenty-five towns have been selected to represent the full range of cardiovascular mortality and water hardness and the major geographic regions. Some 8000 men aged 40 to 59 years drawn from a representative general practice in each town are being studied to relate the prevalence of personal risk factors to cardiovascular mortality. A prospective study will relate incidence of cardiovascular events to personal and environmental risk factors. Preliminary results from the first 16 towns are presented.

Mean systolic and diastolic blood pressures vary widely and there is a strong relation between them and cardiovascular mortality rates in the towns. There is a positive relation between mean blood lead concentrations and mean blood pressures but no relation between water hardness and blood pressures. An inverse relation is seen between respiratory function and cardiovascular mortality rates. No relation is evident between mean plasma total cholesterol or mean high-density lipoprotein levels and cardiovascular mortality and there is little difference between towns in body mass index.

Social class and coronary heart disease

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Forty years ago death from coronary heart disease appeared to be much commoner in professional classes, whereas now it is much commoner in manual and unskilled classes. Changes in diagnostic fashion account for only part of this reversal of the social class pattern. The worsening mortality in lower classes correlates statistically with more smoking and with various dietary changes.

The mortality differential is even wider in our study of 17 530 male London civil servants: in the lowest employment grade the age-adjusted rate is 360 per cent of that in the top (administrative) grade. Part of this large difference can be accounted for by higher levels of smoking and blood pressure and by lower levels of leisure-time exercise, glucose tolerance, and body height; but much of the high coronary heart disease mortality of working-class men remains unexplained.

Socioeconomic factors and coronary heart disease

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The relation between socioeconomic groups, the prevalence of coronary heart disease, and the presence of coronary risk factors was examined in 1568 male subjects who attended an Irish Heart Foundation industrial-based risk factor screening programme. One-third were in the higher and one-sixth were in the lower socioeconomic groups. Social class was defined according to the level of formal education, the subjects being divided into those with first, second, and third level of education.

A history of hypertension, coronary disease, and intermittent claudication was significantly associated with lower socioeconomic class ($p < 0{\cdot}05$ in all cases). These findings may be explained by the distribution of coronary risk factors. Those in the lower socioeconomic group included more current smokers and less non-smokers. They had significantly higher blood pressure and cholesterol levels compared with the better educated groups and they were heavier, older, and exercised less.

Minor ST segment and T wave changes in resting electrocardiogram of asymptomatic subjects

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Minor T wave and ST segment changes in the resting electrocardiogram of asymptomatic subjects are a frequent and non-specific finding. As possible indicators of occult coronary artery disease they may be of significance in the routine examination of professional aircrew.

Routine scrutiny of 14 000 professional aircrew and air-traffic control officers over a two-year period yielded 192 subjects who underwent maximal treadmill electrocardiography at CAA House for the elucidation of possible cardiovascular disease. One hundred and seven (55·7%) of these had minor ST-T changes in the resting electrocardiogram. Further investigation of this group led to the permanent loss of licence in seven (6·5%) on account of proven or strongly suspected coronary artery disease and in one case from hypertrophic obstructive cardiomyopathy. Seven (6·5%) more licences had restrictions imposed on account of borderline exercise responses pending further investigation. Angiography was performed in 11 (10·3%) but only three had significant coronary artery disease. Of the remaining 93, 26 (28·0%) had non-diasgnostic changes on exercise and 40 (43·0%) demonstrated a reduction in T wave voltage ⩾50 per cent on hyperventilation at rest which was corrected by exercise.

It is concluded that minor ST-T changes are unusually caused by coronary artery disease in asymptomatic subjects and that the so-called labile T wave syndrome is considerably more common.

Replacement versus repair for severe mitral regurgitation caused by "floppy" valves

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Between September 1969 and September 1979, 120 patients underwent operation for severe mitral regurgitation caused by "floppy" valves. Valve replacement, using an inverted fresh aortic homograft, was performed in 45 patients (group A) all before 1974 and 75 patients (group B) had repair of their valves. The ages of the patients were between 7 and 71 years (mean 48). Five of the younger patients had Marfan's syndrome and 17 patients had had bacterial endocarditis. There was rapid deterioration in symptoms before operation. Ruptured chordae to the posterior cusp was present in 72 patients (60%), to the anterior cusp in 15. Thirty-three patients had a combination of both, or elongated chordae. There was no significant difference in age, severity of symptoms, or type of lesion found at operation in either group. Additional procedures were performed in three patients in group A and 13 in group B.

The early mortality for isolated repair was 2 per cent compared with 7 per cent for replacement. The overall late mortality was 21 per cent for group A (mean follow-up of 78 months) and 6 per cent for group B (mean follow-up of 38 months). The five-year actuarial survival for group A was 63 per cent and 89 per cent for group B. Twenty-seven patients in group A (93%) and 55 patients in group B (93%) moved to Class I or II of the NYHA Classification.

It is concluded that a valve conserving procedure is possible in almost all patients and appears to give better early and late results.

Identification of risk of thromboembolism from prosthetic cardiac valves

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The use of oral anticoagulants in patients with prosthetic cardiac valves has reduced the risk of thromboembolism. However, 10 per cent of patients with mechanical valves still have thromboemboli despite adequate anticoagulation. Abnormal platelet function has been shown in such patients. A radioimmunoassay for the platelet specific protein betathromboglobulin (BTG) has been developed. The plasma BTG is thought to measure the in vivo platelet aggregation and release reaction occurring at the time of sampling. We have studied 131 patients with valve replacements. Those with double valve replacements had a significantly higher plasma BTG (67·74±5·42 ng/ml $N=18$) than those with single metal valve prostheses (55·5±2·3 ng/ml $N=69$, $p<0{\cdot}05$). In turn, patients with single metal prostheses had significantly raised values compared with those with heterograft valves (45·7±2·3 ng/ml $N=24$, $p<0{\cdot}05$). This is in keeping with the known thrombogenicity of metal valves compared with heterograft valves. Patients with single metal valves who suffered a thromboembolic event while on warfarin had a nearly significantly higher BTG (65·0±4·3 ng/ml $N=13$, $p<0{\cdot}1$) than those with single metal valves who had no thromboemboli. We conclude that raised plasma BTG identifies those patients with prosthetic valves who are at risk from platelet thromboemboli.

Yield of coronary arteriography in patients before valve replacement

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Coronary arteriograms performed before valve replacement in 643 patients (age range 31 to 77 years; mean 54±8 years) were reviewed in order to assess the value of this investigation in patients with valve disease with or without angina.

Significant coronary artery disease was more common in the 199 patients with angina (42%) than in the 444 patients without angina (14%) and was more common in the 417 patients who had one or more coronary heart disease risk factors (31%) than in those without risk factors (8%).

In the patients without angina, significant coronary artery disease was found more frequently in those with at least one risk factor (21%) than in those with no risk factors (4%), and progressively more commonly in those patients with increasing numbers of risk factors. All differences were statistically significant ($p<0{\cdot}001$).

Thus, the yield of abnormal arteriograms in patients in whom both angina and risk factors are absent is very small, whereas the yield becomes significantly greater in those with angina and in angina-free patients who possess risk factors.

Orthotopic heart transplantation after 16 hours of ischaemia

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Preliminary experiments with cardiopulmonary bypass showed that satisfactory preservation of the heart could be obtained for periods of up to four hours of ischaemia using single dose cold cardioplegia and rapid induction of local profound cardiac hypothermia. Thereafter morbidity from prolonged cardiopulmonary bypass became a limiting factor.

The present experiments were designed to test the efficacy of cardioplegia and rapid cooling for prolonged (16 hour) periods of myocardial ischaemia using orthotopic heart transplantation in pigs as the experimental model. The donor heart is excised after infusing cold cardioplegia into the aortic root during venous inflow occlusion and then rapidly cooled and maintained at 2 to 4°C in cardioplegic solution. Sixteen hours later it is transplanted orthotopically into the recipient animal.

Early graft function was good or excellent in 11 of 14 experiments, as judged by these animals being weaned satisfactorily from bypass with minimal inotropic support. Seven pigs subsequently lived between six hours and 83 days, the latter animal being sacrificed electively after immunosuppression with Cyclosporin A.

This simple and effective method for achieving extended periods of myocardial preservation has important implications with regard to heart donor procurement for clinical transplantation.

Value of computer digitisation of left ventricular echocardiogram in transposition of the great arteries

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Thirty-one patients with transposition of the great arteries had sequential M-mode echocardiograms recorded during the first year of life. Twenty-three had further sequential studies after a corrective Mustard procedure. Computer digitisation of left ventricular echocardiograms was carried out and the following indices measured, LVEDD; LVESD; max dd/dt and max dd/dt/d for both ventricular filling and emptying. The results obtained were compared with data from normal infants.

At birth, left ventricular dimensions, filling, and emptying characteristics were normal but all became significantly reduced by 2 months of age, suggesting abnormal left ventricular function. Normal or increased left ventricular dimension and filling/emptying rates were maintained only where there was a duct or ventricular septal defect with associated increased pulmonary blood flow. These abnormalities in left ventricular function indices persisted after a Mustard procedure. In three patients with documented post-Mustard caval obstruction, an extremely slow left ventricular filling profile was recorded, which we consider to be diagnostic of obstructed systemic venous return.

It is concluded that sequential analysis of left ventricular function by digitisation of the M-mode left ventricular echocardiogram is of considerable value in the management of infants with transposition of great arteries as it provides non-invasive evidence of abnormal left ventricular function and allows identification of a ventricular septal defect, persistent ductus arteriosus, or obstructed systemic venous return.

Accuracy of two-dimensional echocardiography in diagnosis of mitral stenosis

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Previous studies have shown a poor correlation between the severity of the degree of mitral valve stenosis using M-mode echocardiography with the haemodynamic assessment of the mitral valve area. The object of this study was to compare two-dimensional echocardiographic assessment with haemodynamic assessment of the mitral valve area in 15 patients with pure mitral stenosis.

Satisfactory two-dimensional echocardiograms of the mitral valve leaflets were obtained in 10 patients with the Smith Kline Instruments EkoSector System I. The echocardiograms were recorded on polaroid film, enlarged by a factor of 10, and the valve area estimated by planimetry. All patients underwent left and right heart catheterisation. Dye dilution cardiac outputs were performed and the mitral valve area was calculated using the Gorlin formula.

The degree of mitral stenosis ranged from trivial to severe (range 2·9 to 0·8 cm^2) with a mean haemodynamic mitral valve area of 1·38 ±0·21 cm^2 (SE) and by two-dimensional echocardiography (range 2·8 to 0·9 cm^2) with a mean of 1·45 ±0·21 cm^2 (SE). There was a linear relation of the valve areas by the two methods with a correlation coefficient of 0·88.

The results suggest the severity of mitral stenosis and the mitral valve area can be accurately assessed non-invasively by two-dimensional echocardiography.

Two-dimensional echocardiographic categorisation of univentricular heart: ventricular morphology, type, and mode of atrioventricular connection

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Most univentricular hearts have two chambers in their ventricular mass, only one of which possesses an atrioventricular connection. Categorisation into univentricular hearts of right or left ventricular type, or indeterminate type, using two-dimensional echocardiography has been successfully achieved in 80 patients to whom this technique has been applied. Thus, right ventricular rudimentary chambers in 59 univentricular hearts of left ventricular type were shown to be anterosuperior and either to right or left. In contrast, left ventricular rudimentary chambers in 10 univentricular heart of right ventricular type were posteroinferior. Eleven univentricular hearts of indeterminate type were characterised by absence of a rudimentary chamber. In addition the trabecular pattern of both main and rudimentary chambers was separately identified in some of the patients with univentricular hearts of right and left ventricular type, and 2-D echocardiography also illustrated the mode of atrioventricular connection, either via two valves, a common valve, or straddling valve, and in the latter demonstrated the orientation of the septum straddled. Finally, it was also possible to distinguish absent atrioventricular connection from an imperforate valve in five patients.

Three-dimensional ambulatory monitoring for arrhythmias

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Ambulatory monitoring of arrhythmias has become established in clinical medicine. The interpretation of single bipolar lead recordings may be difficult because of artefact, and the distinction between supraventricular and ventricular arrhythmias may be impossible. We have obtained three-dimensional recordings (X, Y, and Z co-ordinates) using a modified three-channel Oxford Medilog box. The most suitable of the three recordings is played back through an Oxford unit and Reynolds pathfinder. When an arrhythmia is detected or an artefact such as a dislodged lead is suspected the three lead recordings are played on to a three-channel tape-recorder, which is subsequently played back to display an X, Y, Z electrocardiogram. The best single lead for identification of P wave and QRS can at any time be changed for single lead write-out.

To date we have obtained these recordings in 32 patients. Twenty of these patients had arrhythmias, which were identified as ventricular in 10 and supraventricular in four from X, Y, Z recordings, though single lead recording was not diagnostic. In addition, five patients had one unsatisfactory recording out of the three and the redundancy of leads prevented repetition of the test. It is concluded that three-dimensional ambulatory monitoring is useful for identifying and studying arrhythmias.

Is thallium-201 (^{201}Tl) tomography superior to standard digital ^{201}Tl scintigraphy in detection of patients with coronary artery disease?

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A standard parallel-hole collimator was compared with a multi-pinhole tomographic collimator (12 slices) to evaluate ^{201}Tl myocardial scintigrams acquired during stress and tracer redistribution in 43 patients (14 normal coronary arteries; 12 coronary artery disease; 11 post-coronary artery bypass surgery; six unknown coronary artery status). Tomograms and standard scintigrams were analysed independently from a colour digital display by four observers.

Of the 12 patients with coronary artery disease, 10 had an abnormal standard scintigram compared with nine with an abnormal tomogram (NS). In the 11 patients with coronary artery bypass surgery no preference could be shown for either collimator in the predictive evaluation of graft status or in the detection of ischaemia in diseased but non-grafted coronary arteries. Of the 14 patients with normal coronary arteries only seven had a normal standard scintigram, and eight a normal tomogram (NS). Finally, of the six patients without arteriographic data, five had an abnormal standard scintigram compared with four with an abnormal tomogram (NS). Standard scintigrams and tomograms were completely comparable in the detection of intramyocardial tracer redistribution.

We conclude that ^{201}Tl tomograms are not superior to standard digital scintigrams in the detection of patients with normal and diseased coronary arteries.

Biplane exercise radionuclide ventriculography in patients with coronary artery disease

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Fifteen patients with coronary artery disease were investigated by exercise first pass radionuclide ventriculography in right and left anterior oblique projections. There was a fall in left ventricular ejection fraction (LVEF) on exercise for left anterior oblique ($p<0{\cdot}05$) and right anterior oblique ($p<0{\cdot}05$) projections, with no significant differences between the two obliques. For the eight patients with triple vessel disease mean LVEF fell from 64·1 to 52·5 in the right anterior oblique

($p < 0\cdot01$) and from 49·9 to 40·8 in the left anterior oblique ($p < 0\cdot02$). Fall in LVEF was higher for patients with triple vessel disease than for those with less extensive lesions in right anterior oblique ($p < 0\cdot01$) and left anterior oblique ($p < 0\cdot05$). Rest and exercise regional wall motion abnormalities were assessed; 15/15 zones of exercise-induced regional wall motion abnormalities seen in the right anterior oblique and 21/25 seen in the left anterior oblique were in regions supplied by significantly stenosed vessels. Of 34 coronary artery stenoses, 22 were identified by regional wall motion abnormalities in the left anterior oblique and 22 in the right anterior oblique. Combined right and left anterior oblique analysis identified 28. Six of seven patients with triple vessel disease had a positive exercise study (exercise LVEF $<50\%$, exercise-induced regional wall motion abnormality or fall in LVEF on exercise $>10\%$) in the right anterior oblique, and six of seven in the left anterior oblique. All seven were identified by combined analysis.

Both right and left anterior oblique exercise first pass radionuclide ventriculography are of value in the assessment of patients with coronary artery disease. Biplane radionuclide ventriculography improves the detection of individual stenoses and may prove helpful in the identification of patients with triple vessel disease.

Nifedipine added to beta-blockade: beneficial effect in coronary artery disease

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The haemodynamic and metabolic effects of adding nifedipine to chronic beta-adrenergic blocking therapy were studied before and during atrial pacing to angina in 10 patients. All were taking propranolol 80 mg tds (or equivalent) and had proven extensive coronary artery disease. Heart rate at rest rose from 63 beats/minute on beta-blockade alone to 76 beats/min 20 minutes after nifedipine 20 mg sublingually ($p < 0\cdot02$). Likewise, coronary sinus blood flow rose from 74 ml/min to 127 ml/min ($p < 0\cdot005$) and coronary vascular resistance fell from 1·1 to 0·8 units ($p < 0\cdot005$). Arterio-coronary sinus oxygen difference fell from 5352 to 3568 μmol/l. Cardiac output, total peripheral resistance, systolic blood pressure, and myocardial lactate metabolism were unchanged at rest.

Addition of nifedipine to beta-blockade prolonged pacing time from 363 to 494 seconds.

These results suggest that nifedipine produces an additional beneficial effect on myocardial function in patients with coronary artery disease already on beta-blockade; this appears to be a result in part of a coronary vasodilator property of the drug.

Anti-anginal effects of propranolol and nifedipine

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Using a double blind randomised clinical trial of balanced Latin square design, the antianginal effects of nifedipine (60 mg/day), propranolol (480 mg/day), and the combination were compared with placebo in 16 patients with severe angina pectoris. Response to treatment was assessed by exercise praecordial ST mapping, 48-hour ambulatory electrocardiographic monitoring, pain relief, and glyceryl trinitrate consumption.

There was a decrease in pain frequency from 22 ± 4 attacks per patient per week (mean ± SEM) on placebo to 14 ± 3 (nifedipine), 7 ± 2 (propranolol), and 6 ± 2 (propranolol and nifedipine) ($p < 0\cdot005$, 0·001, and 0·001, respectively).

Objectively, the total area of exercise-induced ST depression was decreased from 20 ± 3 mm per patient (placebo) to 14 ± 3 (nifedipine), 10 ± 2 (propranolol), and $2\pm0\cdot7$ (propranolol and nifedipine) ($p < 0\cdot005$, 0·005, and 0·0005, respectively). Episodes of ST depression detected on ambulatory monitoring were reduced from 7 ± 2 episodes per patient per 24 hours (placebo) to $3\cdot5\pm0\cdot8$ (nifedipine), $1\cdot3\pm0\cdot4$ (propranolol), and $0\cdot25\pm0\cdot2$ (propranolol and nifedipine) ($p < 0\cdot025$, 0·01, and 0·001, respectively).

Resting supine heart rate fell from 75 ± 3 beats/min on placebo to 56 ± 2 on propranolol ($p < 0\cdot0005$) and 57 ± 3 beats/min ($p < 0\cdot0005$) on propranol and nifedipine, but remained unchanged on nifedipine (73 ± 4 beats/min); similar effects were seen on the erect heart rate, the calculated mean rate from monitor tapes, and the maximum rate induced by exercise.

All three active treatments had significant anti-anginal effects, by all criteria; the objective methods of exercise praecordial mapping and ambulatory ST monitoring provided the only reliable indices that propranolol and nifedipine were significantly better than either drug.

Our observations show that the combination is a safe and effective form of treatment for angina.

Prostacyclin: haemodynamic and metabolic effects in patients with ischaemic heart disease

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Prostacyclin is a prostaglandin synthesised within the vascular endothelium. The objectives of this study were to examine the relative effects of an infusion of the drug, at doses of 2, 4, 6, and 8 ng/kg per min, on the coronary and systemic haemodynamics and its inhibition of platelet aggregation in patients with angiographically proven coronary artery disease. Eight patients have been investigated and dose related changes were observed. At 8 ng heart rate increased (71 to 84 beats/minute) while systolic (137 to 111 mmHg) and diastolic (70 to 61 mmHg) pressures fell. Total systemic vascular resistance fell (22·1 to 14·3 units) and cardiac output increased (4·23 to 5·30 l/min). Pulmonary artery pressures were unchanged. Coronary vascular resistance fell from 0·76 to 0·56 units, but the total coronary sinus blood flow was unchanged. Platelet aggregation (Born technique) was inhibited by 45 per cent at 6 ng. Lactate and oxygen extraction were unchanged at rest but pacing time to angina during prostacyclin infusion was prolonged in 60 per cent of patients.

These mild coronary and systemic haemodynamic effects with significant inhibition of platelet aggregation and prolongation of pacing time to angina suggest that prostacyclin should be evaluated in patients with unstable angina.

Autoimmunity—high prevalence in coronary artery disease: possible role in pathogenesis of atheroma

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This study was performed to test the hypothesis that preclinical hypothyroidism is a causative factor in coronary atheroma. Using patients undergoing coronary arteriography, 108 subjects with coronary atheroma were matched for age and sex with 108 subjects with no angiographic evidence of atheroma. At catheterisation each had the following tests: tissue autoantibody, thyroxin, triiodothyronine and thyrotropin releasing hormone stimulation test.

There was a highly significant difference in the prevalence of tissue autoantibody between the two groups (men $p=0·003$, women $p=0·006$).There were 67 men and 41 women in each group; 21 per cent of men (14) with atheroma had autoantibodies compared with 4 per cent of controls (3); 46 per cent of women (19) with atheroma had autoantibodies compared with 20 per cent of controls (8). The type of autoantibody differed between sexes. In women the commonest autoantibodies were against thyroid whereas non-thyroid autoantibodies were predominant in men. No difference in thyroid function was found between the two groups; nor was there any difference in the serum cholesterol between those with normal and abnormal thyroid function.

Incidence studies have suggested that thyroid autoimmunity is a risk factor for coronary artery disease. This study has shown that tissue autoantibody in general is associated with coronary artery disease and it is suggested that autoantibody may promote atheroma through intimal damage resulting from circulating immune complexes.

Heart rate response to glyceryl trinitrate as a test of beta-adrenoceptor blockade: a reappraisal

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The heart rate response to glycerly trinitrate has been claimed to be independent of vagal effects and has been used as a test of beta-adrenoceptor blockade.[1] However, its usefulness has been questioned.[2] Six normal men, mean age 28 ± 1·6 SEM years, had a mean response of 23 ± 1 beats per minute after placing a standard glyceryl trinitrate tablet (0·5 mg) under the tongue for four minutes while standing upright. Blockade of the cardiac autonomic nervous system by intravenous atropine 0·04 mg/kg and practolol 0·6 mg/kg showed that the heart rate response resulted both from vagal withdrawal and reflex sympathetic stimulation of the heart, each contributing 50 per cent of the total heart rate response.

Beta-adrenoceptor antagonism was assessed by inhibition of heart rate response to glyceryl trinitrate and compared with reductions in exercising heart rates in 13 essential hypertensives, mean age 49 ± 2 years, who completed a double blind comparison of placebo, acebutolol 200 mg twice daily, and acebutolol 400 mg once daily. Both tests detected beta-adrenoceptor antagonism at 12 and 24 h after the last dose of active drug and there was a significant correlation between the heart rate responses to both tests (control: $r=0{\cdot}71$, $p<0{\cdot}001$; 12 h: $r=0{\cdot}75$, $p<0{\cdot}001$; 24 h: $r=0{\cdot}74$, $p<0{\cdot}001$). Furthermore, there was a significant correlation between the heart rate response to glyceryl trinitrate and serum acebutolol levels ($r=0{\cdot}60$, $p<0{\cdot}001$). Therefore, the glyceryl trinitrate tests appear to be at least as effective as bicycle exercise in detecting levels of beta-adrenoceptor antagonism.

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Late results of monocusp reconstruction of right ventricular outflow tract in patients with tetralogy of Fallot operated on under 2 years of age

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Seventeen children with tetralogy of Fallot, who underwent successful reconstruction of the right ventricular outflow tract with a monocusp of a fresh adult-sized aortic homograft, have been followed-up for between two and seven years (mean 4·25). Their ages were between 5 and 24 months (mean 13 months). The monocusp was used to enlarge the valve ring and at the same time to render the valve competent. There have been no late deaths and all children are asymptomatic and not on cardiac drugs. Five patients (29%) have developed a soft early diastolic murmur at varying intervals since operation. There is calcification in the free wall of the homograft in all patients. Fifteen patients have been reinvestigated two weeks to 44 months after operation. Five have been reinvestigated twice. Fourteen patients had a right ventricular outflow tract gradient of less than 15 mmHg, and the RV/LV ratio was less than 0·4 in 12 patients. The right ventricular end-diastolic pressure was less than 12 mmHg in all patients. In those patients investigated twice there was no change in right ventricular outflow tract gradient, RV/LV ratio, or right ventricular end-diastolic pressure. No patient had angiographic evidence of significant pulmonary regurgitation.

It is concluded that reconstruction of the right ventricular outflow tract in patients with tetralogy of Fallot, operated upon under the age of 2 years, gives good long-term results and appears to allow for growth.

Infradiaphragmatic total anomalous pulmonary venous drainage: surgical treatment and long-term results

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Since 1971, 20 infants (aged 1 day to 3 months) with infradiaphragmatic total anomalous pulmonary venous drainage have undergone repair. All patients presented with severe cyanosis (mean PaO_2 35·8) and congestive heart failure. Right-sided pressures were equal to or greater than systemic in 18. All had a persistent ductus arteriosus. Surgical repair was accomplished using deep hypothermia with circulatory arrest. The confluence of pulmonary veins was anastomosed to the left atrium. The descending vein was ligated or divided in 15 and left open in five. Atrial septal defects were closed with a patch in six and sutured in 14. Eight patients died (40%). Acidosis upon admission was significantly greater among non-survivors (mean pH 7·29 $+0{\cdot}03$) than survivors (mean pH $7{\cdot}37\pm0{\cdot}02$), $p<0{\cdot}05$. No differences were noted in catheterisation findings, timing of operation, or surgical techniques. Twelve survivors are well two months to seven years after operation. All are asymptomatic and none requires cardiac medication. Normal chest *x*-rays and cardiac rhythms are present in each. Five have undergone repeat catheterisation, demonstrating normal pressures and no shunts. It is concluded that the initial mortality of infradiaphragmatic total anomalous pulmonary venous drainage depends mainly upon the condition of the child on admission. Long-term results of surviving patients are excellent.

Filter films in infants with heart disease

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Determination of atrial situs is of cardinal importance in the analysis of complex congenital heart lesions, and is best predicted from bronchial situs.

However, previous methods for assessing bronchial morphology are unsuited to the very young patient.

To assess bronchial morphology, 100 consecutive patients under 18 months of age (median 2 months) with suspected congenital heart disease were studied by high kilovoltage filtered beam radiographs, before cardiac catheterisation. This low radiation dose technique clearly defined bronchial anatomy in 95 patients. Bronchial lengths were compared and 10 cases had a ratio $<1{\cdot}5$ suggesting situs ambiguus. Discriminant function analysis based on tracheal width and bronchial length enabled clear distinction of right from left bronchi. Four patients had bilateral right and six had bilateral left bronchi. Three of these 10 cases died and there was necropsy confirmation of the radiological diagnosis.

Thus routine screening of bronchial situs in this age group has shown an unexpectedly high incidence (10%) of situs ambiguus. This is known to be associated with a constellation of cardiac anomalies, most importantly interrupted inferior vena cava with left isomerism and total anomalous pulmonary venous drainage with right isomerism. This simple technique therefore provides a useful basis for planning cardiac catheterisation.

Severe apnoea and prolonged duct patency after use of prostaglandin E_2

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The use of E-type prostaglandins to maintain patency of the ductus arteriosus in the ductus dependent pulmonary blood circulation is well established. Their use has been suggested to facilitate safe transfer of certain groups of critically sick and cyanosed neonates to regional centres. We report here complications of prostaglandin infusion in six patients (three pulmonary atresia with intact septum, two pulmonary atresia with ventricular septal defect, one tetralogy of Fallot) presenting in the first few days of life with severe cyanosis ($PO_2 < 5$kPa).

All received prostaglandin E_2 (PGE_2) 0·05 to 0·1 μg/kg per min via a peripheral vein and a rise in arterial PO_2 resulted $\geqslant 3$ kPa. Three of four patients breathing spontaneously developed recurrent apnoea during PGE_2 infusion and one required ventilation. None had been apnoeic previously, and no other cause for apnoea was found.

A modified right Blalock Taussig anastomosis (five cases) or Waterston-Cooley anastomosis (one case) was performed within 24 hours of admission, and the PGE_2 infusion discontinued 24 hours postoperatively. Four cases were considered to have persistent duct patency after stopping PGE_2. In two of these with intractable pulmonary oedema, wide duct patency was confirmed two to three weeks later at subsequent operation to close the ductus. Both the apnoeic episodes and prolonged ductal patency were considered to be related to use of prostaglandin E_2.

Notices

Br Heart J 1980; **43:** 728

Manuscripts are invited on cardiac surgical subjects. Preference will be shown for articles concentrating on short- or long-term results, free from unnecessary technical detail and containing a clear message of value to cardiological physicians and surgeons.

Annual Meeting of the Society of Nuclear Medicine

The 18th Annual Meeting of the Society of Nuclear Medicine will take place in September 1980 in Erlangen/Nürnberg.

For information and submission of papers: Professor Dr F Wolf, 18th International Annual Meeting, Society of Nuclear Medicine, Institut und Poliklinik für Nuklearmedizin der Universität Erlangen-Nürnberg, Krankenhausstrasse 12, D-8500 Erlangen. Tel: 09131/8534 11, 8534 16.

Fourth Symposium on Echocardiology

The fourth symposium on echocardiology will be held at the Erasmus University, Rotterdam, The Netherlands, on 24 to 26 June 1981.

Deadline for abstracts 15 September 1980. Authors of accepted abstracts are requested to submit a manuscript.

For further details, please write to: Fourth Symposium on Echocardiology, Erasmus University Ee 2302a, PO Box 1738, 3000 DR Rotterdam, The Netherlands. Attn Mr H Rijsterborgh.

Third Annual Seminar on Fundamental Cardiology

The third annual seminar on fundamental cardiology, organised by the French Society of Cardiology under the patronage of the European Society of Cardiology will be held at the laboratories of Merck Sharp & Dohme—Chibret at Clermont-Ferrand on 22 to 24 January 1981. The theme of the 1981 meeting will be peripheral circulation. The delegates must be less than 35 years, be fluent in English and/or French, and must submit an application including details of their studies, their official hospital and university appointments, and a recommendation from the head of the department. Applications must be received by 15 September 1980. There is no registration fee.

All correspondence should be addressed to: Professor Rene Gourgon, Secretary of the Seminar of Fundamental Cardiology, Hopital Beaujon, 100 bld du General Leclerc, 92118 Clichy Cedex, France.

IX World Congress of Cardiology

The congress will be held from 20 to 26 June 1982 in Moscow. It is being organised by The Society of Cardiology of the USSR; and sponsored by The International Society and Federation of Cardiology, The Union of the Soviet Socialist Republics, Moscow.

The opening and closing ceremonies are to take place at the Kremlin Palace of Congresses. The scientific sessions will be held in eight auditoriums situated in three buildings close to one another in the centre of the city.

The scientific programme, which has been drawn up with the active participation of the Scientific Councils of the International Society and Federation of Cardiology, will include almost all the main aspects of modern cardiology. Aerospace cardiology will be discussed for the first time and molecular and preventive cardiology will be dealt with in greater detail. The programme will include the following: (1) Lectures; (2) symposia and round table discussions; (3) free communications; (4) posters; (5) scientific films.

The deadline for the receipt of abstracts will be announced in the next communication.

Correspondence to: Congress Secretariat: Dr R G Oganov, Secretary General, The USSR Cardiology Research Center, Petroverigski per., 10, Moscow 101837, USSR. Cable address: USSR Moscow K-62 IX Cardiology.

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Antihyperlipoproteinaemic treatment: Easier done than said?

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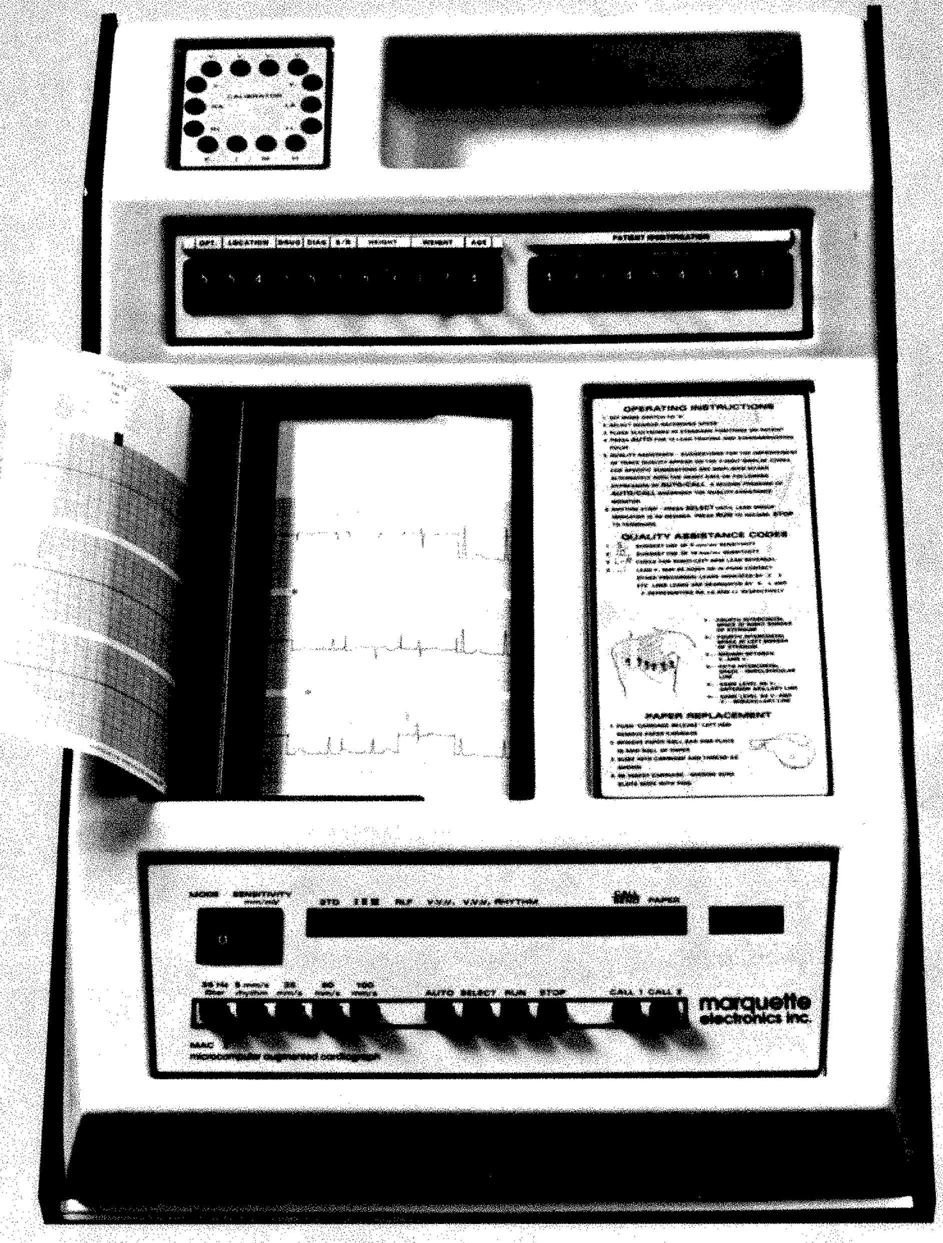

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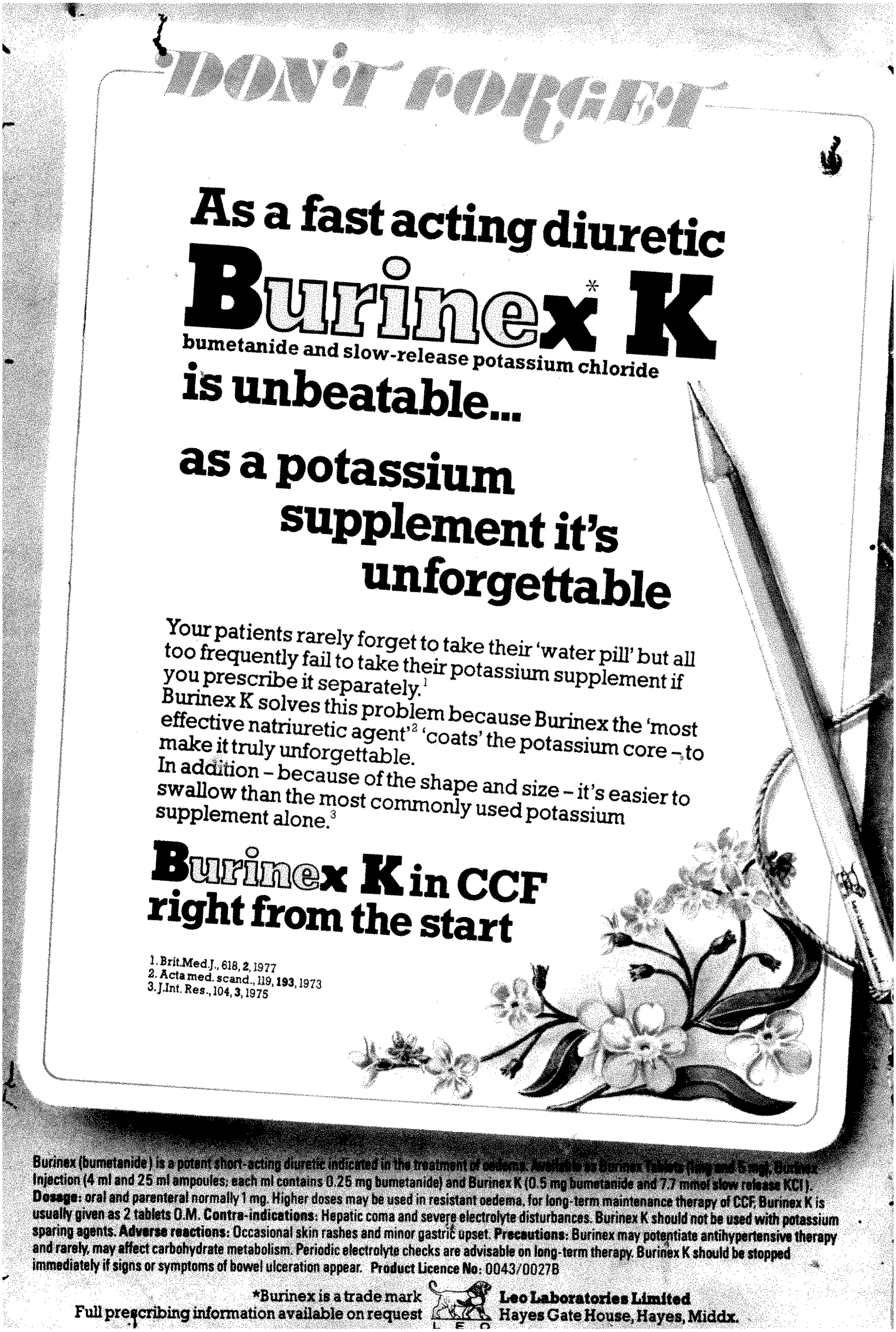

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